poly(isobutyl methacrylate), poly(alginate), poly(amide), and poly(silicone). The polymers and manufacturing procedures are known in Polymers, by Coleman *et al.*, Vol. **31**, pp. 1187-1230 (1990); *Drug Carrier Systems*, by Roerdink *et al.*, Vol. 9, pp. 57-109 (1989); *Adv. Drug Delivery Rev.*, by Leong *et al.*, Vol. 1, pp. 199-233 (1987); *Handbook of Common Polymers*, Compiled by Roff *et al.*, (1971) published by CRC Press; and U.S. Pat. No. 3,992,518.

Other exemplary embodiments of the delivery devices are described in the subsection below, and in the Example section of the application.

**Other Exemplary Delivery Devices and Systems**

This subsection describes additional exemplary delivery systems that can be used to deliver any of a large spectrum of compounds (*e.g.*, drugs, prodrugs, metabolic precursors, *etc.*), especially those with limited absorption windows in upper GI (*e.g.*, stomach).

An exemplary list of compounds that can be delivered using the subject dosage forms and/or delivery devices includes, but not limited to: metformin, acyclovir, ranitidine, riboflavin, chlorthiazide, gabapentin, losartin potassium, ganciclovir, cimetidine, minocycline, fexofenadine, bupropion, orlistat, captopril, diphenhydramine, tripelennamine, chlorpheniramine maleate, promethazine, omeprazole, prostaglandin, carbenoxolane, sucralphate, isosorbide, quinidine, enalapril, nifedipine, verapamil, diltiazem, nadolol, timolol, pindolol, salbutamol, terbutaline, carbuterol, broxaterol, aminophylline, cyclizine, cinnarizine, domperidone, alizapride, vincristine, megestrol acetate, daunorubicin, actinomycin, adriamycin, etoposide, 5-fluorouracil, indomethacin, sulindac, piroxicam, ibuprofen, naproxen, ketoprofen, temazepam, lorazepam, flunitrazepam, amantadine, ampicillin, amoxicillin, erythromycin, tetracyclines, cyanocobalamin, amino acids, iron or calcium salts of essential trace elements, or pharmacologically acceptable salts of the above.

In certain embodiments of the invention, illustrated in **Figure 22**, the oral solid dosage form is a monolayer matrix tablet **100**, containing one or more drug(s), pharmaceutically acceptable excipients or salts thereof, optionally one or more permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in a single monolithic layer **110**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR) or controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from all sides. The cross-section of this dosage form is illustrated in **Figure 22.**

In certain embodiments of the invention, illustrated in **Figure 23,** the oral solid dosage form is a bilayer tablet **200,** containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in two monolithic layers **210** and **220.** Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In these embodiments, the tablet is designed to provide immediate release (IR) or controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from layer **210,** and optionally an extended release (ER) of one or more soluble drugs from the other layer **220.** One or more bioadhesive polymer compositions are incorporated into layer **220.** This layer may optionally contain release rate controlling polymer(s), pore former(s), and/or other polymer(s) to regulate its rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 23.**

In certain embodiments of the invention, illustrated in **Figure 24,** the oral solid dosage form is a trilayer tablet **300,** containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in three monolithic layers **310, 320** and **330.** Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In these embodiments, the tablet is designed to provide controlled release (CR) of one or more soluble, poorly soluble or insoluble drug from layer **310,** and optionally an extended release (ER) of one or more soluble drugs from the other layers **320** and **330.** One or more bioadhesive polymer compositions may be incorporated into layers **320** and **330.** These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 24.**

In certain embodiments of the invention, illustrated in **Figure 25,** the oral solid dosage form is a trilayer tablet with a pre-compressed insert **400,** containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in three layers **410, 420** and **430,** and a pre-compressed tablet **440,** inserted in layer **410.** Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer and the pre-compressed insert. In this embodiment, the tablet is designed to provide ascending controlled release (aCR) of one or more poorly soluble or insoluble drugs

from layer **410** and pre-compressed insert **440,** and optionally an extended release (ER) of one or more soluble drugs from layers **420** and **430**. One or more bioadhesive polymer compositions may be incorporated into layers **420** and **430**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 25.**

In certain embodiments of the invention, illustrated in **Figure 26,** the oral solid dosage form is a trilayer tablet **500**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in three monolithic layers **510, 520** and **530**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In these embodiments, the tablet layers are designed to provide immediate release (IR) layer **520**, and/or controlled release (CR) layer **510**, of one or more soluble, poorly soluble or insoluble drugs, and optionally an extended release (ER) layer **530**, of one or more soluble drugs. One or more bioadhesive polymer compositions are incorporated into layer **530**. This layer may option-ally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate its rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 26.**

In certain embodiments of the invention, illustrated in **Figure 27,** the oral solid dosage form is a trilayer tablet with a pre-compressed insert **600**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in three layers **610, 620** and **630**, and a pre-compressed tablet **640**, inserted in layer **610**, laying approximately on the middle of the bottom layer **630**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer and the pre-compressed insert. In this embodiment, the tablet layers and the pre-compressed insert are designed to provide immediate release (IR) from layer **620**, and ascending controlled release (aCR) from layer **610** and pre-compressed insert **640**, of one or more soluble, poorly soluble or insoluble drug, and optionally an extended release (ER), from layer **630,** of one or more soluble drugs. One or more bioadhesive polymer compositions is incorporated into layer **630**. This layer may contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate its rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 27.**

In certain embodiments of the invention, illustrated in **Figure 28**, the oral solid dosage form is a quadrilayer tablet **700**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in four monolithic layers **710**, **720**, **730** and **740**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet layers are designed to provide immediate release (IR), from layer **720**, and controlled release (CR), from layer **710**, of one or more soluble, poorly soluble or insoluble drugs, and optionally an extended release (ER), from layers **730** and/or **740**, of one or more soluble drugs. One or more bioadhesive polymer compositions is incorporated into layers **730** and **740**. These layers may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 28**.

In certain embodiments of the invention, illustrated in **Figure 29**, the oral solid dosage form is a quadrilayer tablet with a pre-compressed insert **800**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in four monolithic layers, **810**, **820**, **830** and **840**, and a pre-compressed tablet **850**, inserted in the center of layer **810**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer and the pre-compressed insert. In this embodiment, the tablet layers are designed to provide immediate release (IR), from layer **820**, and ascending controlled release (aCR), from layer **810** and pre-compressed insert **850**, of one or more soluble, poorly soluble or insoluble drug, and optionally an extended release (ER), layers **830** and/or **840**, of one or more soluble drug. One or more bioadhesive polymer compositions is incorporated into layers **830** and **840**. These layers may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 29**.

In certain embodiments of the invention, illustrated in **Figure 30**, the oral solid dosage form is a monolayer matrix tablet, **900**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single monolithic layer **910**. The tablet may be optionally coated with a

release rate-controlling membrane **920**, before applying the bioadhesive coating membrane **930**. Optionally the release rate-controlling and bioadhesive membranes, **920** and **930**, may have plasticizer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of the core tablet and the coating membrane(s). In this embodiment, the tablet is designed to provide controlled release (CR) of one or more soluble, poorly soluble or insoluble drug from all sides. The cross-section of this dosage form is illustrated in **Figure 30**.

In certain embodiments of the invention, illustrated in **Figure 31**, the oral solid dosage form is a monolayer tablet with a pre-compressed insert **1000**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single layer **1010**, and a pre-compressed tablet **1020**, inserted in the center of that layer. The tablet may be optionally coated with a release rate-controlling membrane **1030**, before applying the bioadhesive coating membrane **1040**. Optionally the release rate-controlling and bioadhesive membranes **1030** and **1040**, may have plasticizer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of the core tablet and the coating membrane(s). In this embodiment, the tablet is designed to provide controlled release (CR) or ascending controlled release (aCR) of one or more soluble, poorly soluble or insoluble drug from all sides. The cross-section of this dosage form is illustrated in **Figure 31**.

In certain embodiments of the invention, illustrated in **Figure 32**, the oral solid dosage form is a trilayer tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **1100**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in three layers, **1110**, **1120** and **1130**, and granulated, spheronized, pelletized, or mini-tableted multiparticulates **1140**, dispersed in layer **1110**. The multiparticulates are film-coated with one or more bioadhesive polymer compositions **1150**. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive pellets. The top-coat membrane may serve different purposes, including functioning as a moisture

and/or oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying layer **1110**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide controlled release (CR) of one or more soluble, poorly soluble or insoluble drug from bioadhesive multiparticulates **1140/1150** and possibly layer **1110**, and optionally an extended release (ER) of one or more soluble drug from layers **1120** and/or **1130**. One or more bioadhesive polymer compositions is incorporated into layers **1120** and **1130**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 32**.

In certain embodiments of the invention, illustrated in **Figure 33**, the oral solid dosage form is a trilayer tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **1200**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in three layers, **1210**, **1220** and **1230**, and granulated, spheronized, pelletized, or mini-tableted multiparticulates **1240**, dispersed in layer **1210**. The multiparticulates are film-coated with one or more bioadhesive polymer compositions **1250**. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive pellets. The top-coat membrane may serve different purposes, including functioning as a moisture and/or oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying layer **1210**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR), from layer **1220**, and controlled release (CR), from bioadhesive multiparticulates **1240/1250** and possibly layer **1210**, of one or more soluble, poorly soluble or insoluble drug, and optionally an extended release (ER) of one or more soluble drug from layers **1240** and/or **1250**. One or more bioadhesive polymer compositions is incorporated into layers **1240** and **1250**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 33**.

In certain embodiments of the invention, illustrated in **Figure 34,** the oral solid dosage form is a quadrilayer tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **1300**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in four layers, **1310**, **1320**, **1330**, and **1340**, and granulated, spheronized, pelletized, or mini-tableted multiparticulates **1350**, dispersed in layer **1310**. The multiparticulates are film-coated with one or more bioadhesive polymer compositions **1360**. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive multiparticulates. The top-coat membrane may serve different purposes, including functioning as a moisture and/or oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying layer **1310**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer and the multiparticulates. In this embodiment, the tablet is designed to provide immediate release (IR), from layer **1320**, and controlled release (CR), from bioadhesive multiparticulates **1350/1360** and possibly layer **1310**, of one or more soluble, poorly soluble or insoluble drug, and optionally an extended release (ER) of one or more soluble drug from layers **1330** and/or **1340**. One or more bioadhesive polymer compositions is incorporated into layers **1330** and **1340**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 34**.

In certain embodiments of the invention, illustrated in **Figure 35,** the solid oral dosage form is a longitudinally compressed tablet **1400**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single monolithic layer **1410**. The tablet is sealed peripherally with a layer of bioadhesive composition **1420**, leaving the upper and lower sides, **1430A** and **1430B**, of the tablet available for drug release. Optionally, the tablet may be coated with a release rate-controlling layer before applying the bioadhesive coating. Optionally, the release rate-controlling and bioadhesive coatings may have plasticizer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. Various drug release profiles, and

preferably and more advantageously, zero-order release profiles, can be achieved by tailoring the composition of the core matrix. The cross-section of this dosage form is illustrated in **Figure 35.**

In certain embodiments of the invention, illustrated in **Figure 36,** the solid oral dosage form is a longitudinally compressed tablet **1500,** containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in two monolithic layers, **1510** and **1520.** The tablet is sealed peripherally with a layer of bioadhesive composition **1530,** leaving the upper and lower sides, **1540A** and **1540B,** of the tablet available for drug release. Optionally, the bioadhesive coating may have plasticizer(s), pore former(s), and other polymer(s) to regulate its rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR) of one or more soluble, poorly soluble or insoluble drugs from layer **1510,** and controlled release (CR) of one or more soluble drugs from the other layer **1520.** The cross-section of this dosage form is illustrated in **Figure 36.**

In certain embodiments of the invention, illustrated in **Figure 37,** the solid oral dosage form is a longitudinally compressed tablet **1600,** containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in four monolithic layers, **1610, 1620, 1630** and **1640.** The tablet is sealed peripherally with a layer of bioadhesive composition **1650,** leaving the upper and lower sides, **1660A** and **1660B,** of the tablet available for drug release. Optionally, the bioadhesive coating may have plasticizer(s), pore former(s), and other polymer(s) to regulate its rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR) of one or more soluble, poorly soluble or insoluble drugs from layer **1610,** and controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from layer **1640,** followed by fast release of one or more soluble, poorly soluble or insoluble drugs from layer **1640.** Layers **1610** and **1630** are separated by a slow dissolving passive matrix **1620,** which may completely dissolve following the depletion of drug(s) from layer **1640.** The cross-section of this dosage form is illustrated in **Figure 37.**

In certain embodiments of the invention, illustrated in **Figure 38,** the solid oral

dosage form is a longitudinally compressed tablet **1700**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in four monolithic layers, **1710**, **1720**, **1730** and **1740**. The tablet is sealed peripherally with a layer of bioadhesive composition **1750**, leaving the upper and lower sides, **1760A** and **1760B**, of the tablet available for drug release. Optionally, the bioadhesive coating may have plasticizer(s), pore former(s), and other polymer(s) to regulate its rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR) or fast controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from layer **1710**, followed by delayed release of one or more soluble, poorly soluble or insoluble drugs from layer **1730** in an immediate release (IR) or fast controlled release (CR) fashion. Layer **1740** is a slow dissolving passive matrix **1720**, which completely dissolves following the depletion of drug(s) from layer **1710**. Layers **1710** and **1730** are separated by a slow dissolving passive matrix **1720**, which may completely dissolve following the depletion of drug(s) from layers **1710** and **1730**. The cross-section of this dosage form is illustrated in **Figure 38**.

In certain embodiments of the invention, illustrated in **Figure 39**, the oral solid dosage form **1800**, is a hard shell two-piece capsule **1810**, containing a monolayer matrix tablet **1820**, and a trilayer tablet **1830**. The monolayer tablet **1820**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single layer matrix. The trilayer tablet **1830**, contains one or more drug, pharmaceutically acceptable excipients, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in three monolithic layers, **1840**, **1850** and **1860**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each tablet. In this embodiment, the tablets are designed to provide immediate release (IR) of one or more soluble, poorly soluble or insoluble drugs from monolayer tablet **1820**, and controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from trilayer tablet **1830**. One or more bioadhesive polymer compositions is incorporated into layers **1850** and **1860**. These layers may have identical or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and

permeability. The cross-section of this dosage form is illustrated in **Figure 39**.

In certain embodiments of the invention, illustrated in **Figure 40**, the oral solid dosage form **1900**, is a hard shell two-piece capsule **1910**, containing a multiplicity of monolayer matrix tablets, **1920**, **1930**, **1940**, **1950**, and **1960**. The monolayer tablets, contains one or more drug, pharmaceutically acceptable excipients, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single layer matrix. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each tablet. In this embodiment, the tablets are designed to provide immediate release (IR) and controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs. The cross-section of this dosage form is illustrated in **Figure 40**.

In certain embodiments of the invention, illustrated in **Figure 41**, the oral solid dosage form is a quadrilayer tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **2000**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in four layers, **2010**, **2020**, **2030**, and **2040**, and granulated, spheronized, pelletized, or mini-tableted multiparticulates, **2050**, **2060 and 2070**, respectively dispersed in layers **2020**, **2030**, and **2040**. The multiparticulates may be optionally film-coated with one or more bioadhesive polymer compositions. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive pellets. The top-coat membrane may serve different purposes, including functioning as a moisture and/or oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying layers. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer and the multiparticulates. In this embodiment, the tablet is designed to provide immediate release (IR), from layer **2010**, and controlled release (CR), from multiparticulates **2050** and possibly layer **2020**, of one or more soluble, poorly soluble or insoluble drug. Optionally one or more soluble, poorly soluble or insoluble drug is released from the multiparticulates **2060** and **2070**, and their respective layers, **2030** and **2040**, in an extended release (ER) fashion. One or more bioadhesive polymer compositions is incorporated into layers **2060** and **2070**. These layers may have same or different compositions, and may optionally contain release rate

controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 41**.

In certain embodiments of the invention, illustrated in **Figure 42,** the oral solid dosage form is a monolayer tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **2100**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions. The tablet is formulated as a single rapidly disintegrating matrix **2110**, and contains a solid dispersion of granulated, spheronized, pelletized, or mini-tableted multiparticulates **2120**. The multiparticulates are film-coated with one or more bioadhesive polymer compositions **2130**. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive multiparticulates. The top-coat membrane may serve different purposes, including functioning as a moisture and/or oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying matrix **2110**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of the matrix and the multiparticulates. In this embodiment, the tablet is designed to provide immediate release (IR), from matrix **2110**, and controlled release (CR), from bioadhesive multiparticulates **2120/2130**, of one or more soluble, poorly soluble or insoluble drug. The cross-section of this dosage form is illustrated in **Figure 42**.

These various embodiments are only a sample of numerous possible configurations to deliver the subject dosage forms. Other variations may be readily envisioned based on the principals and teachings of the instant specification.

In these and other embodiments of the invention, the various bioadhesive coatings that can be used are described in detail in the section below. The terms "bioadhesive polymer composition" and "bioadhesive polymer material" is intended to encompass both compositions where the polymer itself is bioadhesive, as well as compositions where a non- or poorly bioadhesive polymer is combined with a compound that imparts bioadhesive properties to the composition as a whole, as described in detail herein.

Preferably, other than the desired immediate release doses, drug eluting devices of the invention release the drug or prodrug contained therein with zero-order kinetics.

Many of the different embodiments described above may be implemented by using

rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a subject pharmaceutical composition at a particular target site.

In certain embodiments, representative dosage forms include hydrogel matrix containing a plurality of tiny pills or other particles (see **Figure 2**). The hydrogel matrix comprises a hydrophilic polymer, such as selected from a polysaccharide, agar, agarose, natural gum, alkali alginate including sodium alginate, carrageenan, fucoidan, furcellaran, laminaran, hypnea, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust bean gum, pectin, amylopectin, gelatin and a hydrophilic colloid. The hydrogel matrix comprises a plurality of tiny pills or particles (such as 4 to 50), each tiny pill or particle may comprise a different ratio of decarboxylase inhibitor / levodopa, either as first or second IR or the second zero-order release portion, *etc.* The tiny pills or particles may comprise a release rate controlling wall of 0.01 mm to 10 mm thickness to provide for the timed release of drug in different portions. Representative of wall-forming materials include a triglyceryl ester selected from glyceryl tristearate, glyceryl monostearate, glyceryl dipalmitate, glyceryl laureate, glyceryl didecenoate and glyceryl tridecenoate. Other wall forming materials comprise polyvinyl acetate phthalate, methylcellulose phthalate, and microporous vinyl olefins. Procedures for manufacturing tiny pills are disclosed in U.S. Pat. Nos. 4,434,153; 4,721,613; 4,853,229; 2,996,431; 3,139,383 and 4,752,470, which are incorporated by reference herein.

In certain embodiments, the drug-releasing beads are characterized by a dissolution profile wherein 0 to 20% of the beads undergo dissolution and release the drug in 0 to 2 hours, 20 to 40% undergo dissolution and release the drug in 2 to 4 hours, 40 to 60% exhibit dissolution and release in 4 to 6 hours, 60 to 80% in 6 to 8 hours, and 80 to 100% in 8 to 10 hours or longer. The drug-releasing beads can include a central composition or core comprising a drug and pharmaceutically acceptable composition forming ingredients including a lubricant, antioxidant, and buffer. The beads comprise increasing doses of drug, for example, 0.1 mg, 0.2 mg, 0.5 mg, and so forth to a high dose. The beads are coated with a release rate-controlling polymer that can be selected utilizing the dissolution profile disclosed above. The manufacture of the beads can be adapted from, for example, Liu *et al.*, *Inter. J. of Pharm.* **112**: 105-116, 1994; Liu *et al.*, *Inter. J. of Pharm.* **112**: 117-124, 1994;

*Pharm. Sci.*, by Remington, 14th Ed. pp. 1626-1628 (1970); Fincher *et al.*, *J. Pharm. Sci.* 57: 1825-1835, 1968; and U.S. Pat. No. 4,083,949.

Another dosage form provided by the invention comprises a multiplicity of layers (see **Figures 1, 3, 4, *etc.***). The phrase "multiplicity of layers" typically denotes 2 to 6 layers in contacting lamination (can be more layers if necessary). The multiplicity of layers are positioned consecutively, that is, one layer after another in order, with a first exposed layer, the sixth layer in contact with the fifth layer and its exposed surface coated with a drug impermeable polymer. The sixth layer is coated with a drug impermeable polymer to insure release of the subject pharmaceutical composition from the first layer to the sixth layer. The biodegradable polymers undergo chemical decomposition to form soluble monomers or soluble polymer units. The biodegradation of polymers usually involves chemically or enzymatically catalyzed hydrolysis. Representative of biodegradable polymers acceptable for an increase drug loading in each layer of from 5 to 50 wt % over the first and successive layers wherein the first layer comprises 100 ng. Representative biodegradable polymers comprise a member selected from biodegradable poly(amides), poly(amino acids), poly(esters), poly(lactic acid), poly(glycolic acid), poly(orthoesters), poly(anhydrides), biodegradable poly(dehydropyrans), and poly(dioxinones). The polymers are known to the art in Controlled Release of Drugs, by Rosoff, Ch. 2, pp. 53-95 (1989); and in U.S. Pat. Nos. 3,811,444; 3,962,414; 4,066,747; 4,070,347; 4,079,038; and 4,093,709.

In still other embodiments, the invention employs a dosage form comprising a polymer that releases a drug by diffusion, flux through pores, or by rupture of a polymer matrix. The drug delivery polymeric system delivers a substantially zero-order release portion of the pharmaceutical composition may optionally comprise an inhibitor / levodopa ratio gradient, wherein the gradient is, for example, a descent in inhibitor / levodopa ratio from a beginning or initial ratio to a final, or lower ratio (comparably less inhibitor). The dosage form comprises an exposed surface at the beginning dose and a distant nonexposed surface at the final dose. The nonexposed surface is coated with a pharmaceutically acceptable material impermeable to the passage of drug. The dosage form structure provides for a delivery of drug at a relatively sustained level, with an optionally changing (*e.g.*, decreasing) inhibitor / levodopa ratio from the beginning to the final delivered dose of the second portion of the dosage form. The ratio may also be different in the first and second (if present) IR (or other substantially ascending dose portion) according to the instant invention.

The dosage form matrix can be made by procedures known to the polymer art. In one manufacture, 3 to 5 or more casting compositions are independently prepared wherein each casting composition comprises a portion of the dosage form, with each portion overlayered from, for example, a high to low inhibitor / levodopa ratio in the zero-order release dosage portion (second portion). This provides a series of layers that come together to provide a unit polymer matrix with an optionally varying inhibitor / levodopa ratio gradient. In another manufacture, the lower ratio portion is cast first followed by laminating with layers of ascending ratio portions to provide a polymer matrix with an inhibitor / levodopa ratio gradient. An example of providing a dosage form comprises blending a pharmaceutically acceptable carrier, like polyethylene glycol, with a known dose of the subject pharmaceutical composition, and adding it to a silastic medical grade elastomer with a cross-linking agent, like stannous octanoate, followed by casting in a mold. The step is repeated for each successive layer. The system is allowed to set, *e.g.*, for 1 hour, to provide the dosage form. Representative polymers suitable for manufacturing the dosage form include olefin and vinyl polymers, condensation polymers, carbohydrate polymers, and silicon polymers as represented by poly(ethylene), poly(propylene), poly(vinyl acetate), poly(methyl acrylate), poly(isobutyl methacrylate), poly(alginate), poly(amide), and poly(silicone). The polymers and manufacturing procedures are known in Polymers, by Coleman *et al.*, Vol. 31, pp. 1187-1230 (1990); *Drug Carrier Systems*, by Roerdink *et al.*, Vol. 9, pp. 57-109 (1989); *Adv. Drug Delivery Rev.*, by Leong *et al.*, Vol. 1, pp. 199-233 (1987); *Handbook of Common Polymers*, Compiled by Roff *et al.*, (1971) published by CRC Press; and U.S. Pat. No. 3,992,518.

In yet other embodiments, the subject pharmaceutical compositions are delivered by way of a transdermal patch, a buccal patch, or a buccal tablet. A patch is generally a flat hollow device with a permeable membrane on one side and also some form of adhesive to maintain the patch in place on the patient's skin, with the membrane in contact with the skin so that the medication can diffuse out of the patch reservoir and into and through the skin. The outer side of the patch is formed of an impermeable layer of material, and the membrane side and the outer side are joined around the perimeter of the patch, forming a reservoir for the medication and carrier between the two layers.

Patch technology is based on the ability to hold an active ingredient in constant contact with the epidermis. Over substantial periods of time, drug molecules, held in such a state, will eventually find their way into the bloodstream. Thus, patch technology relies on

the ability of the human body to pick up drug molecules through the skin. Transdermal drug delivery using patch technology has recently been applied for delivery of nicotine, in an effort to assist smokers in quitting, the delivery of nitroglycerine to angina sufferers, the delivery of replacement hormones in post-menopausal women, *etc.* These conventional drug delivery systems comprise a patch with an active ingredient such as a drug incorporated therein, the patch also including an adhesive for attachment to the skin so as to place the active ingredient in close proximity to the skin. Exemplary patch technologies are available from Ciba-Geigy Corporation and Alza Corporation. Such transdermal delivery devices can be readily adapted for use with the subject pharmaceutical compositions.

The flux of the subject pharmaceutical compositions across the skin can be modulated by changing either (a) the resistance (the diffusion coefficient), or (b) the driving force (the solubility of the drug in the stratum corneum and consequently the gradient for diffusion). Various methods can be used to increase skin permeation by the subject reuptake inhibitors, including penetration enhancers, use of pro-drug versions, superfluous vehicles, iontophoresis, phonophoresis, macroflux with micro projections, and thermophoresis. Many enhancer compositions have been developed to change one or both of these factors. See, for example, U.S. Pat. Nos. 4,006,218; 3,551,154; and 3,472,931, for example, respectively describe the use of dimethylsulfoxide (DMSO), dimethyl formamide (DMF), and N,N-dimethylacetamide (DMA) for enhancing the absorption of topically applied drugs through the stratum corneum. Combinations of enhancers comprising diethylene glycol monoethyl or monomethyl ether with propylene glycol monolaurate and methyl laurate are disclosed in U.S. Pat. No. 4,973,468. A dual enhancer comprising glycerol monolaurate and ethanol for the transdermal delivery of drugs is shown in U.S. Pat. No. 4,820,720. U.S. Pat. No. 5,006,342 lists numerous enhancers for transdermal drug administration comprising fatty acid esters or fatty alcohol ethers of C2 to C4 alkanediols, where each fatty acid/alcohol portion of the ester/ether is of about 8 to 22 carbon atoms. U.S. Pat. No. 4,863,970 shows penetration-enhancing compositions for topical application comprising an active permeant contained in a penetration-enhancing vehicle containing specified amounts of one or more cell-envelope disordering compounds such as oleic acid, oleyl alcohol, and glycerol esters of oleic acid; a C2 or C3 alkanol; and an inert diluent such as water. Other examples are included in the teachings of U.S. Pat. No. 4,933,184 which discloses the use of menthol as a penetration enhancer; U.S. Pat. No. 5,229,130 discloses the use of vegetable oil (soybean and/or coconut oil) as a penetration enhancer; and U.S. Pat. No. 4,440,777 discloses the use

of eucalyptol as a penetration enhancer.

The patch preferably comprises a drug-impermeable backing layer. Suitable examples of drug-impermeable backing layers which may be used for transdermal or medicated patches include films or sheets of polyolefins, polyesters, polyurethanes, polyvinyl alcohols, polyvinyl chlorides, polyvinylidene chloride, polyamides, ethylene-vinyl acetate copolymer (EVA), ethylene-ethylacrylate copolymer (EEA), vinyl acetate-vinyl chloride copolymer, cellulose acetate, ethyl cellulose, metal vapor deposited films or sheets thereof, rubber sheets or films, expanded synthetic resin sheets or films, non-woven fabrics, fabrics, knitted fabrics, paper and foils. Preferred drug-impermeable, elastic backing materials are selected from polyethylene terephthalate (PET), polyurethane, ethylene-vinyl acetate copolymer (EVA), plasticized polyvinylchloride, woven and non-woven fabric. Especially preferred is non-woven polyethyleneterephthalate (PET). Other backings will be readily apparent to those skilled artisan.

The dosage formulations described above, in the forms of cores of tablets and drug eluting devices of the invention, contain one or more excipients, carriers or diluents. These excipients, carriers or diluents can be selected, for example, to control the disintegration rate of a tablet or drug eluting device to fit the desired release profile according to the instant invention. In addition, the one or more carriers (additives) and/or diluents may be pharmaceutically acceptable.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filter, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject regulators from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum

hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

Typical excipients to be added to a capsule formulation include, but are not limited to: fillers such as microcrystalline cellulose, soy polysaccharides, calcium phosphate dihydrate, calcium sulfate, lactose, sucrose, sorbitol, or any other inert filler. In addition, there can be flow aids such as fumed silicon dioxide, silica gel, magnesium stearate, calcium stearate or any other materials that impart good flow properties. A lubricant can also be added if desired, such as polyethylene glycol, leucine, glyceryl behenate, magnesium stearate or calcium stearate.

In certain embodiments, the disintegration time of a particular composition (such as the immediate release composition) may be less than the gastric (or small/large intestinal) retention time. In one embodiment, the disintegration time of a tablet is at least 25% of the gastric retention time, at least 50% of the gastric retention time or at least 75% of the gastric retention time. In other embodiments, the disintegration time of a composition may be formulated to effect a substantially zero-order release, over a period of 2, 4, 6, 8, 12, or 24 hours, for instance.

The formulations can conveniently be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy. All methods include bringing into association the drug with the carrier or diluent which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the agent with the carriers and then, if necessary, dividing the product into unit dosages thereof. It will be understood by those skilled in the art that any vehicle or carrier conventionally employed and which is inert with respect to the active agent, and preferably does not interfere with bioadhesiveness, may be utilized for preparing and administering the pharmaceutical compositions of the present invention. Illustrative of such vehicles and carriers are those described, for example, in *Remington's Pharmaceutical Sciences*, 18th ed. (1990), the disclosure of which is incorporated herein by reference.

Examples of carriers and diluents include pharmaceutically accepted hydrogels such as alginate, chitosan, methylmethacrylates, cellulose and derivatives thereof (microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose, ethylcellulose), agarose and Povidone™, kaolin, magnesium stearate, starch, lactose, sucrose, density-controlling agents such as barium sulfate and oils,

dissolution enhancers such as aspartic acid, citric acid, glutamic acid, tartartic acid, sodium bicarbonate, sodium carbonate, sodium phosphate, glycine, tricine, Tromethamine, and TRIS.

The excipients, carriers or diluents can also be selected to control the time until a dosage form detaches from a mucosal membrane. In particular, the addition of one or more disintegrating agents will reduce the time until a tablet or drug eluting device detaches. Alternatively or in combination with the disintegrating agents, an agent that interferes with the mucosa-tablet / device adhesion can be used to control the time until detachment occurs.

As set out above, certain embodiments of the present pharmaceutical compositions may contain a basic functional group, such as amino or alkylamino, and are thus capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable acids. The term "pharmaceutically acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include but are not limited to following: 2-hydroxyethanesulfonate, 2-naphthalenesulfonate, 3-hydroxy-2-naphthoate, 3-phenylpropionate, acetate, adipate, alginate, amsonate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bisulfate, bitartrate, borate, butyrate, calcium edetate, camphorate, camphorsulfonate, camsylate, carbonate, citrate, clavulariate, cyclopentanepropionate, digluconate, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, fumarate, gluceptate, glucoheptanoate, gluconate, glutamate, glycerophosphate, glycollylarsanilate, hemisulfate, heptanoate, hexafluorophosphate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, laurylsulphonate, malate, maleate, mandelate, mesylate, methanesulfonate, methylbromide, methylnitrate, methylsulfate, mucate, naphthylate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, palmitate, pamoate, pantothenate, pectinate, persulfate, phosphate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosaliculate, suramate, tannate, tartrate, teoclate, thiocyanate, tosylate, triethiodide, undecanoate, and valerate salts, and the like. (See, for example, Berge *et al.*, "Pharmaceutical Salts", *J. Pharm. Sci.* **66**: 1-19, 1977).

In certain embodiments, the pharmaceutically acceptable salts of the subject compounds include the conventional non-toxic salts of the compounds, *e.g.*, from non-toxic organic or inorganic acids. Particularly suitable are salts of weak acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, hydriodic, cinnamic, gluconic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, maleic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared in situ during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, and magnesium salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, tromethamin, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge *et al.*, *supra*).

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Pharmaceutically acceptable antioxidants may also be included. Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-

tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

VII. *Controlled Release / Bioadhesive Layer*

In certain embodiments of the invention, the subject dosage form is administered orally to the gastrointestinal (GI) tract. In such embodiments, it is desirable that the drug not be delivered substantially beyond the desired site of action and eliminated before it has had a chance to exert a topical effect or to pass into the bloodstream, particularly in the context of avoiding the gastric emptying and its adverse contribution to the On-Off effect. Thus, it is desirable that the subject drug delivery system adhere to the lining of the appropriate viscus, such that its contents can be delivered as a function of proximity and duration of contact.

An orally ingested product can adhere to either the epithelial surface or the mucus lining of the GI tract. For the delivery of bioactive substances, it can be advantageous to have a polymeric drug delivery device adhere to the epithelium or to the mucous layer. Bioadhesion in the GI tract may proceed in two stages: (1) viscoelastic deformation at the point of contact of the synthetic material into the mucus substrate, and (2) formation of bonds between the adhesive synthetic material and the mucus or the epithelial cells. In general, adhesion of polymers to tissues may be achieved by (i) physical or mechanical bonds, (ii) primary or covalent chemical bonds, and/or (iii) secondary chemical bonds (*e.g.*, ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bioadhesive properties, include dispersive interactions (*e.g.*, van der Waals interactions) and stronger specific interactions, which include hydrogen bonds. The hydrophilic functional groups primarily responsible for forming hydrogen bonds are the hydroxyl and the carboxylic groups.

In certain embodiments, the subject dosage forms having increased gastrointestinal retention time. For purposes of this invention, gastric residence time is the time required for a dosage form to transit through the stomach to the pyloric sphincter. For example, a dosage form of the invention has a gastric residence time of at least 3 hours, at least 4 hours, at least 6 hours, at least 8 hours or at least 12 hours. The dosage forms of the invention may also have an increased retention time in the small and/or large intestine, or in the area of the gastrointestinal tract that absorbs the drug contained in the dosage form. For example, dosage forms of the invention can be retained in the small intestine (or one or two portions thereof, selected from the duodenum, the jejunum and the ileum) for at least 6 hours, at least

8 hours or at least 12 hours, such as from 16 to 18 hours. For dosage forms having an enteric coating or an equivalent, the increased gastric residence time may not be applicable. These dosage forms, as a whole, include a bioadhesive polymeric coating that is applied to at least one surface of the tablet or drug eluting device.

Certain polymers for use in the subject invention are described in more details below.

Polymers

**I. Bioadhesives**

**a. Polymers**

Suitable bioadhesive polymeric coatings are disclosed in U.S. Patent Nos. 6,197,346, 6,217,908 and 6,365,187 (the contents of which are incorporated herein by reference), and include soluble and insoluble, biodegradable and nonbiodegradable polymers. These can be hydrogels or thermoplastics, homopolymers, copolymers or blends, and/or natural or synthetic polymers. The preferred polymers are synthetic polymers, with controlled synthesis and degradation characteristics. Particularly preferred polymers are anhydride copolymers of fumaric acid and sebacic acid (P(FA:SA)), which have exceptionally good bioadhesive properties when administered to the GI tract. Examples of P(FA:SA) copolymers include those having a 1:99 to 99:1 ratio of fumaric acid to sebacic acid, such as 5:95 to 75:25, for example, 10:90 to 60:40 or at least 15:85 to 25:75. Specific examples of such copolymers have a 20:80 or a 50:50 ratio of fumaric acid to sebacic acid.

Polymers used in dosage forms of the invention produce a bioadhesive interaction (fracture strength) of at least 100 $N/m^2$ (10 $mN/cm^2$) when applied to the mucosal surface of rat intestine. The fracture strength of the dosage forms is advantageously at least 250 $N/m^2$, at least 500 $N/m^2$ or at least 1000 $N/m^2$. For example, the fracture strength of a polymer-containing dosage form can be from 100 to 500 $N/m^2$. The forces described herein refer to measurements made upon rat intestinal mucosa, unless otherwise stated. The same adhesive measurements made on a different species of animal will differ from those obtained using rats. This difference is attributed to both compositional and geometrical variations in the mucous layers of different animal species as well as cellular variations in the mucosal epithelium. However, the data shows that the same general trends prevail no matter what animal is studied (*i.e.*, P(FA:SA) produces stronger adhesions than polylactic acid (PLA) in rats, sheep, pigs, *etc.*). For example, the fracture strength of dosage forms of the invention on rat intestine is generally at least 125 $N/m^2$, such as at least 150 $N/m^2$, at least 250 $N/m^2$,

at least 500 $N/m^2$ or at least 1000 $N/m^2$.

The fracture strength of a dosage form can be measured according to the methods disclosed by Duchene *et al.* Briefly, the dosage form is attached on one side to a tensile tester and is contacted with a testing surface (*e.g.*, a mucosal membrane) on the opposite surface. The tensile tester measures the force required to displace the dosage form from the testing surface. Common tensile testers include a Texture Analyzer and the Instron tensile tester.

In the preferred method for mucoadhesive testing, dosage forms are pressed using flat-faced tooling, 0.3750" (9.525 mm) in diameter. Dosage form weight will depend on composition; in most cases, the dosage forms have a final weight of 200 mg. These dosage forms are then glued to a plastic 10 mm diameter probe using a common, fast-drying cyanoacrylate adhesive. Once the dosage forms are firmly adhered to the probe, the probe is attached to the Texture Analyzer. The Texture Analyzer is fitted with a 1 kg load cell for maximum sensitivity. The following settings are used:

| | | | |
|---|---|---|---|
| Pre-Test Speed | 0.4 mm / sec | Stop Plot At | Final Position |
| Test Speed | 0.1 mm / sec | Tare Mode | Auto |
| Post-Test Speed | 0.1 mm / sec | Delay Acquisition | Off |
| Applied Force | 20.0 g | Advanced Options | On |
| Return Distance | 0 mm | Proportional Gain | 0 |
| Contact Time | 420 s | Integral Gain | 0 |
| Trigger Type | Auto | Differential Gain | 0 |
| Trigger Force | 0.5 g | Max. Tracking Speed | 0 mm / sec |

The Test and Post-Test Speeds are as low as the instrument will allow, to ensure a maximum number of data points captured. The Pre-Test speed is used only until the probe encounters the Trigger Force; *i.e.*, prior to contacting the tissue.

The Proportional, Integral, and Differential Gain are set to 0. These settings, when optimized, maintain the system at the Applied Force for the duration of the Contact Time. With soft tissue as a substrate, however, the probe and dosage form are constantly driven into the deformable surface. This results in visible damage to the tissue. Thus, the probe and dosage form are allowed to relax gradually from the Applied Force by setting these parameters to 0. The tracking speed, which is a measure of how rapidly the feedback is adjusted, is also set to 0.

The tissue on which the dosage forms are tested is secured in the Mucoadhesive Rig;

the rig is then completely immersed in a 600 mL Pyrex beaker containing 375 mL of PBS. The tissue is maintained at approximately 37°C for the duration of the test; no stirring is used as the machine can detect the oscillations from the stir bar.

In the past, two classes of polymers have shown useful bioadhesive properties, hydrophilic polymers and hydrogels. In the large class of hydrophilic polymers, those containing carboxylic groups (*e.g.*, poly[acrylic acid]) exhibit the best bioadhesive properties. It is thus expected that polymers with the highest concentrations of carboxylic groups are preferred materials for bioadhesion on soft tissues. In other studies, the most promising polymers were sodium alginate, carboxymethylcellulose, hydroxymethylcellulose and methylcellulose. Some of these materials are water-soluble, while others are hydrogels.

Rapidly bioerodible polymers such as poly[lactide-co-glycolide], polyanhydrides, and polyorthoesters, whose carboxylic groups are exposed on the external surface as their smooth surface erodes, are particularly suitable for bioadhesive drug delivery systems. In addition, polymers containing labile bonds, such as polyanhydrides and polyesters, are well known for their hydrolytic reactivity. Their hydrolytic degradation rates can generally be altered by simple changes in the polymer backbone.

Representative natural polymers suitable for the present invention include proteins (*e.g.*, hydrophilic proteins), such as zein, modified zein, chitin, chitosan, casein, gelatin, gluten, serum albumin, or collagen, and polysaccharides such as cellulose, dextrans, polyhyaluronic acid, polymers of acrylic and methacrylic esters and alginic acid. These are generally less suitable for use in bioadhesive coatings due to higher levels of variability in the characteristics of the final products, as well as in degradation following administration. Synthetically modified natural polymers include alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, and nitrocelluloses.

Representative synthetic polymers for use in bioadhesive coatings include polyphosphazines, poly(vinyl alcohols), polyamides, polycarbonates, polyalkylenes, polyacrylamides, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and copolymers thereof. Other polymers suitable for use in the invention include, but are not limited to, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl

cellulose, cellulose triacetate, cellulose sulfate sodium salt, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly (ethylene terephthalate), poly(vinyl acetate), polyvinyl chloride, polystyrene, polyvinyl pyrrolidone, and polyvinylphenol. Representative bioerodible polymers for use in bioadhesive coatings include polylactides, polyglycolides and copolymers thereof, poly(ethylene terephthalate), poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), poly[lactide-co-glycolide], polyanhydrides (*e.g.*, poly(adipic anhydride)), polyorthoesters, blends and copolymers thereof.

Polyanhydrides are particularly suitable for use in bioadhesive delivery systems because, as hydrolysis proceeds, causing surface erosion, more and more carboxylic groups are exposed to the external surface. However, polylactides erode more slowly by bulk erosion, which is advantageous in applications where it is desirable to retain the bioadhesive coating for longer durations. In designing bioadhesive polymeric systems based on polylactides, polymers that have high concentrations of carboxylic acid are preferred. The high concentrations of carboxylic acids can be attained by using low molecular weight polymers (MW of 2000 or less), because low molecular weight polymers contain a high concentration of carboxylic acids at the end groups.

The polymers listed above can be obtained from sources such as Sigma Chemical Co., St. Louis, Mo., Polysciences, Warrenton, Pa., Aldrich, Milwaukee, Wis., Fluka, Ronkonkoma, N.Y., and BioRad, Richmond, Calif., or can alternatively be synthesized from monomers obtained from these suppliers using standard techniques.

When the bioadhesive polymeric coating is a synthetic polymer coating, the synthetic polymer is typically selected from polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid), poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends, and copolymers of thereof. Preferably, the synthetic polymer is poly(fumaric-co-sebacic) anhydride.

Another group of polymers suitable for use as bioadhesive polymeric coatings are

polymers having a hydrophobic backbone with at least one hydrophobic group pendant from the backbone. Suitable hydrophobic groups are groups that are generally non-polar. Examples of such hydrophobic groups include alkyl, alkenyl and alkynyl groups. Preferably, the hydrophobic groups are selected to not interfere and instead to enhance the bioadhesiveness of the polymers.

A further group of polymers suitable for use as bioadhesive polymeric coatings are polymers having a hydrophobic backbone with at least one hydrophilic group pendant from the backbone. Suitable hydrophilic groups are groups that are capable of hydrogen bonding to another functional group. Example of such hydrophilic groups include negatively charged groups such as carboxylic acids, sulfonic acids and phosponic acids, positively charged groups such as (protonated) amines and neutral, polar groups such as amides and imines. Preferably, the hydrophilic groups are selected to not interfere and instead to enhance the bioadhesiveness of the polymers. The hydrophilic groups can be either directly attached to a hydrophobic polymer backbone or attached through a spacer group. Typically, a spacer group is an alkylene group, particularly a $C_1$-$C_8$ alkyl group such as a $C_2$-$C_6$ alkyl group. Preferred compounds containing one or more hydrophilic groups include amino acids (*e.g.*, phenyalanine, tyrosine and derivatives thereof) and amine-containing carbohydrates (sugars) such as glucosamine.

Polymers can be modified by increasing the number of carboxylic groups accessible during biodegradation, or on the polymer surface. The polymers can also be modified by binding amino groups to the polymer. The polymers can be modified using any of a number of different coupling chemistries available in the art to covalently attach ligand molecules with bioadhesive properties to the surface-exposed molecules of the polymeric microspheres.

The attachment of any positively charged ligand, such as polyethyleneimine or polylysine, to a polymer may improve bioadhesion due to the electrostatic attraction of the cationic groups coating the beads to the net negative charge of the mucus. The mucopolysaccharides and mucoproteins of the mucin layer, especially the sialic acid residues, are responsible for the negative charge coating. Any ligand with a high binding affinity for mucin could also be covalently linked to most polymers with the appropriate chemistry, such as with carbodiimidazole (CDI), and be expected to influence the binding to the gut. For example, polyclonal antibodies raised against components of mucin or else intact mucin, when covalently coupled to a polymer, would provide for increased

bioadhesion. Similarly, antibodies directed against specific cell surface receptors exposed on the lumenal surface of the intestinal tract would increase the residence time when coupled to polymers using the appropriate chemistry. The ligand affinity need not be based only on electrostatic charge, but other useful physical parameters such as solubility in mucin or specific affinity to carbohydrate groups.

The covalent attachment of any of the natural components of mucin in either pure or partially purified form to the polymers would increase the solubility of the polymer in the mucin layer. The list of useful ligands would include but not be limited to the following: sialic acid, neuraminic acid, n-acetyl-neuraminic acid, n-glycolylneuraminic acid, 4-acetyl-n-acetylneuraminic acid, diacetyl-n-acetylneuraminic acid, glucuronic acid, iduronic acid, galactose, glucose, mannose, fucose, any of the partially purified fractions prepared by chemical treatment of naturally occurring mucin, *e.g.*, mucoproteins, mucopolysaccharides and mucopolysaccharide-protein complexes, and antibodies immunoreactive against proteins or sugar structure on the mucosal surface.

The attachment of polyamino acids containing extra pendant carboxylic acid side groups, such as polyaspartic acid and polyglutamic acid, may also increase bioadhesiveness. The polyamino chains would increase bioadhesion by means of chain entanglement in mucin strands as well as by increased carboxylic charge.

In certain embodiments, certain polymers suitable for the subject invention may be blended with catechol or a catechol derivative. Such polymers may be any non-biodegradable or biodegradable polymer. The polymers can be homopolymers or copolymers. The polymers that are copolymers can be block, alternating or random copolymers. The backbone of the bioadhesive polymer is preferably flexible in order to penetrate mucus and/or epithelial tissue. In the preferred embodiment, the polymer is a hydrophobic polymer. In one embodiment, the polymer is a biodegradable polymer and is used to form an oral dosage formulation.

Examples of biodegradable polymers suitable for use in the invention include synthetic polymers such as poly hydroxy acids, such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyesters, polyurethanes, poly(butyric acid), poly(valeric acid), poly(caprolactone), poly(hydroxybutyrate), poly(lactide-co-glycolide) and poly(lactide-co-caprolactone), and natural polymers such as alginate and other polysaccharides, collagen, chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications

routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein, modified zein, chitin, chitosan, and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo*, by surface or bulk erosion. The foregoing materials may be used alone, as physical mixtures (blends), or as co-polymers. In one aspect of the invention, a bioadhesive polymer is formed by first coupling a compound to a monomer and then polymerizing the coupled monomer. In this embodiment, the monomers are polymerized to form a polymer, including biodegradable and non-biodegradable polymers. Suitable polymers include, but are not limited to: polyanhydrides, polyamides, polycarbonates, polyalkylenes, polyalkylene oxides such as polyethylene glycol and poloxamers, polyalkylene terepthalates such as poly(ethylene terephthalate), polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyethylene, polypropylene, poly(vinyl acetate), poly vinyl chloride, polystyrene, polyvinyl halides, polyvinylpyrrolidone, polyhydroxy acids, polysiloxanes, polyurethanes and copolymers thereof, modified celluloses, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, chitosan, chitin, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, and polyacrylates such as poly(methacrylate) poly(methyl methacrylate), poly(ethylmethacrylate), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecylmethacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate) and poly(octadecyl acrylate).

In some embodiments, one can use non-biodegradable polymers, especially hydrophobic polymers. Examples of preferred non-biodegradable polymers include ethylene vinyl acetate, poly(meth)acrylic acid, copolymers of maleic anhydride with other unsaturated polymerizable monomers, poly(butadiene maleic anhydride), polyamides, copolymers and mixtures thereof, and dextran, cellulose and derivatives thereof.

Hydrophobic polymers include polyanhydrides, poly(ortho)esters, and polyesters such as polycaprolactone. In the preferred embodiment, the polymer is sufficiently hydrophobic that it is not readily water soluble, for example, the polymer should be soluble up to less than about 1% w/w in water, preferably about 0.1% w/w in water, at room

temperature or body temperature. In the most preferred embodiment, the polymer is a polyanhydride, such as a poly(butadiene maleic anhydride) and other copolymers of maleic anhydrides.

Polyanhydrides may be formed from dicarboxylic acids as described in U.S. Patent No. 4,757,128 to Domb *et al.* Suitable diacids include: aliphatic dicarboxylic acids, aromatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, combinations of aromatic, aliphatic and aromatic-aliphatic dicarboxylic acids, aromatic and aliphatic heterocyclic dicarboxylic acids, and aromatic and aliphatic heterocyclic dicarboxylic acids in combination with aliphatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, and aromatic dicarboxylic acids of more than one phenyl group. Suitable monomers include sebacic acid (SA), fumaric acid (FA), bis(p-carboxyphenoxy)propane (CPP), isophthalic acid (IPh), and dodecanedioic acid (DD).

For materials in which the monomer or polymer has been modified, a wide range of molecular weights are suitable for the polymer that forms the backbone of the bioadhesive material. The molecular weight may be as low as about 200 Da (for oligomers) up to about 2,000 kDa. Preferably the polymer has a molecular weight of at least 1,000 Da, more preferably at least 2,000 Da, most preferably the polymer has a molecular weight of up to 20 kDa or up to 200 kDa. The molecular weight of the polymer may be up to 2,000 kDa. For polymers that are blended with catechol or a catechol derivative, the molecular weight is in the range of 20,000 to 1,000,000 Daltons, preferably 20,000 to 200,000 Daltons.

For materials in which the monomer or polymer has been modified, the range of substitution on the polymer varies greatly and depends on the polymer used and the desired bioadhesive strength. For example, a butadiene maleic anhydride copolymer that is 100% substituted with DOPA will have the same number of DOPA molecules per chain length as a 67% substituted ethylene maleic anhydride copolymer. Typically, the polymer has a percent substitution ranging from 10% to 100%, preferably greater than 50%, ranging up to 100%.

The polymers and copolymers that form the backbone of the bioadhesive material contain reactive functional groups which interact with the functional groups on the aromatic compound. Where the aromatic compound is blended with one or more polymers, the polymers preferably have functional groups that do not react with the functional groups of the aromatic compound.

**b. Reactive Functional Groups**

For the polymers modified with a catechol functionality, it is important that the polymer or monomer that forms the polymeric backbone contains accessible functional groups that readily react with functional groups contained in the aromatic compounds, such as amines and thiols. In a preferred embodiment, the polymer contains amino reactive moieties (*i.e.*, moieties that react with an amine, preferably to form a covalent linkage), such as aldehydes, ketones, carboxylic acid derivatives, anhydrides (*e.g.* cyclic anhydrides), alkyl halides, acyl azides, isocyanates, isothiocyanates, and succinimidyl esters.

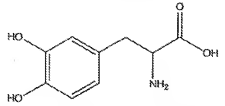
**c. Sidechains containing Aromatic groups with one or more hydroxyl groups**

Aromatic groups containing one or more hydroxyl groups are attached to the polymeric backbone. The aromatic groups may be part of a compound that is grafted to the polymer backbone or the aromatic groups may be part of larger sidechains which are grafted to the polymer backbone. In the preferred embodiment, the aromatic group containing one or more hydroxyl groups is catechol or a derivative thereof. Optionally the aromatic compound is a polyhydroxy aromatic compound, such as a trihydroxy aromatic compound (*e.g.*, phloroglucinol) or a multihydroxy aromatic compound (*e.g.*, tannin). The aromatic moiety can also be an aromatic moiety that includes two or more (*e.g.*, three or more) hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, more typically, hydroxyl substituents or substituents hydrolyzable to hydroxyl substituents. A substituent hydrolyzable to a hydroxyl substituent is a substituent, which when cleaved by water (optionally mediated by an enzyme), that leaves a hydroxyl substituent attached to the phenyl ring. Common examples of such substituents include esters (-O-C(O)-R), carbamates (-O-C(O)-NRR') and carbonates (-O-C(O)-OR).

The catechol derivative may also contain a reactive group, such as an amino, thiol, or halide group. Suitable sidechains, which can be grafted to the polymer backbone, include poly (amino acids), peptides, or proteins, having a molecular weight of 20 kDa or less, where at least 10% of the amino acids contain catechol or catechol-like residues. Preferably greater than 50%, more preferably 75%, and most preferably 100% of the amino acids contain catechol residues. Common amino acids with catechol-like residues are phenylalanine, tyrosine and tryptophan. Additionally, synthetic amino acids that contain catechol residues may be prepared.

A preferred catechol derivative is 3,4-dihydroxyphenylalanine (DOPA), which

contains a primary amine. L-DOPA is known to be pharmaceutically active and is used as a treatment for Parkinson's disease. Tyrosine, the immediate precursor of DOPA, which differs only by the absence of one hydroxyl group in the aromatic ring, can also be used. Tyrosine is capable of conversion (*e.g.* by hydroxylation) to DOPA.




**3,4-dihydroxyphenylalanine (DOPA)**

In a preferred embodiment, the aromatic group is an amine-containing aromatic compound, such as an amine-containing catechol derivative. Other suitable compounds for forming blends include 3,4-dimethoxyphenyl-2-hydrazino-2-methyl propanoic acid, 2-aminocarbonyl-amino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid, 2-amino-3-(3,4-dimethoxyphenyl)-2-methyl hydrochloride, 2-amino-3-(3,4-dimethoxyphenyl)-2-methyl propane nitrile, methyl-DOPA, 3-O-methylcarbidopa and 4-O-methylcarbidopa, and enantiomers and mixtures thereof.

In another preferred embodiment, the aromatic group is a compound comprising:

a) an aromatic moiety comprising two or more hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, and

b) a primary or secondary amino moiety,

where the cumulative amount of the compound (*i.e.*, compound not functionalized to a polymer backbone) that is converted to dopamine when infused into rat striatum is at least 65% less than for an equimolar amount of L-3,4-dihydroxyphenylalanine or where the blood-brain barrier is substantially impermeable to the compound. In certain embodiments, the compounds used to form residues are selected such that the cumulative amount of the compound converted to dopamine when infused into rat striatum is at least 70%, 75%, 80%, 85%, 90%, 95% or 100% (*i.e.*, the compound is not converted to dopamine) less than an equimolar amount of L-3,4-dihydroxyphenylalanine. The cumulative amount of a compound converted to dopamine when infused into rat striatum can be measured according to the method described in Brannan, *et al.*, *Brain Res.* 718:165-168 (1996), the contents of which are incorporated herein by reference. Briefly, a microdialysis probe is lowered into the corpus striatum of anesthetized rats. The probe generally has a tip length of 3 mm and is

perfused with an artificial cerebrospinal fluid solution. Concentrations of dopamine in the microdialysis samples are monitored at regular intervals by HPLC or another suitable analytical method. Once the dopamine concentration reaches a basal level, a 1 mM solution of a sidechain residue compound is perfused into the striatum via the probe, with continued monitoring of the dopamine concentration.

Separately or in addition to selection of aromatic compounds based upon their ability to be converted into dopamine, aromatic compounds can be selected such that the blood-brain barrier is substantially impermeable to these compounds when present as free molecules (*i.e.*, not covalently attached to a polymer). Typically, less than 10%, such as less than 5%, 4%, 3%, 2% or 1%, of a substantially impermeable compound is able to cross the blood-brain barrier. A suitable assay for determining permeability of the blood-brain barrier to a compound is described by Gomes and Soeares-da-Silva in *Brain Res.* 829:143-150 (1999), the contents of which are incorporated herein by reference. Briefly, the assay measures the uptake of a compound by immortalized rat capillary cerebral endothelial cells (RBE 4), which represent the blood-brain barrier. The endothelial cells are seeded in collagen-treated 24-well plastic culture clusters (16 mm internal diameter) at a density of 40,000 cells per well (20,000 cells/cm$^2$). For 24 hours prior to an experiment, the cell medium is free of fetal bovine serum and basic fibroblast growth factor. Uptake experiments are typically performed 6 days after seeding. On the day of the experiment, the growth medium is aspirated and the cells are washed with Hanks' medium at 4 °C, followed by incubating the cells in Hanks' medium at 37 °C for 30 minutes. The cells are incubated for 6 minutes with 2 mL of 1 μM substrate (*e.g.*, sidechain residue compound) in Hanks' medium. Uptake is terminated by rapid removal of uptake solution with a vacuum pump connected to a Pasteur pipette, followed by a rapid wash with cold Hanks' medium and the addition of 250 μL of 0.2 mM perchloric acid. The acidified samples are stored under appropriate conditions until the substrate concentration is measured (*e.g.*, via HPLC).

In another embodiment, the aromatic compounds include all sidechain residue compounds having the moieties discussed above, except L-DOPA and/or DL-DOPA.

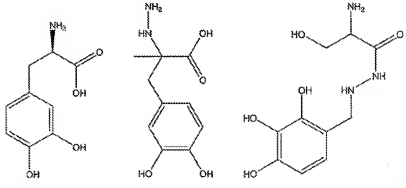
Typically, the aromatic moiety is a monocyclic aromatic moiety that includes two or more hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, more typically, hydroxyl substituents or substituents hydrolyzable to hydroxyl substituents. Preferably, the aromatic moiety is a phenyl moiety that includes two or more (*e.g.*, three or more) hydroxyl substituents, methoxy substituents,

substituents hydrolyzable to hydroxyl substituents, or a combination thereof, more typically, hydroxyl substituents or substituents hydrolyzable to hydroxyl substituents. An exemplary aromatic moiety is catechol. The aromatic moiety can include other substituents in addition to those indicated, but typically does not include additional substituents.

A substituent hydrolyzable to a hydroxyl substituent is a substituent, which when cleaved by water (optionally mediated by an enzyme), that leaves a hydroxyl substituent attached to the phenyl ring. Common examples of such substituents include esters (-O-C(O)-R) and carbonates (-O-C(O)-OR).

The primary or secondary amino moiety can be directly attached to a carbon atom or can be part of a hydrazinyl moiety (-NH-NHR).

Suitable compounds for forming residues include D-3,4-dihydroxyphenylalanine (D-DOPA), (D-, L- or a mixture thereof) carbidopa and (D-, L-, or a mixture thereof) benserazide, which have the following structures, respectively:



Other suitable compounds for forming residues include 3,4-dimethoxyphenyl-2-hydrazino-2-methyl propanoic acid, 2-aminocarbonyl-amino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid, 2-amino-3-(3,4-dimethoxyphenyl)-2-methyl hydrochloride, 2-amino-3-(3,4-dimethoxyphenyl)-2-methyl propane nitrile, methyl-DOPA, 3-O-methylcarbidopa and 4-O-methylcarbidopa, including enantiomers and mixtures thereof.

**d. Blends containing a catechol or a catechol derivative**

In one embodiment, the catechol or catechol derivative is blended with a biodegradable or non-biodegradable polymer to form a bioadhesive composition. The polymer is preferably a hydrophobic polymer. Suitable hydrophobic polymers include ethyl cellulose, poly(anhydrides), and polyesters. The preferred catechol derivatives are 3,4-dihydroxyphenylalanine (DOPA), which contains a primary amine, or carbidopa. The catechol derivative can be present in an amount from about 0.5% to about 95% by weight of the polymer. For example, blending polycaprolactone with L-DOPA in a ratio of 2:1 w/w

results in a bioadhesive material with an adhesive force of 491 $mN/cm^2$ compared to 50 $mN/cm^2$ for polycaprolactone alone.

**II. Method of forming Bioadhesives**

Three general methods are used to form the bioadhesive materials. In one embodiment, a compound containing an aromatic group which contains one or more hydroxyl groups is grafted onto a polymer. In this embodiment, the polymeric backbone is a biodegradable polymer. In a second embodiment, the aromatic compound may be coupled to individual monomers and then polymerized. In a third embodiment, the polymer is blended with a compound containing an aromatic group which contains one or more hydroxyl groups.

Any chemistry which allows for the conjugation of a polymer or monomer to an aromatic compound containing one or more hydroxyl groups may be used. For example, if the aromatic compound contains an amino group and the monomer or polymer contains an amino reactive group, this modification to the polymer or monomer is performed through a nucleophilic addition or a nucleophilic substitution reaction, such as a Michael-type addition reaction, between the amino group in the aromatic compound and the polymer or monomer. Additionally, other procedures can be used in the coupling reaction. For example, carbodiimide and mixed anhydride based procedures form stable amide bonds between carboxylic acids or phosphates and amino groups, bifunctional aldehydes react with primary amino groups, bifunctional active esters react with primary amino groups, and divinylsulfone facilitates reactions with amino, thiol, or hydroxy groups.

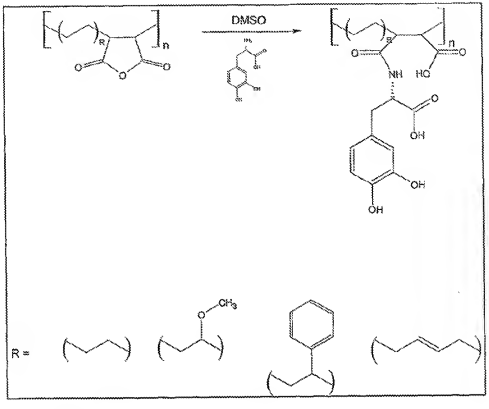
**a. Polymer Grafting**

The aromatic compounds are grafted onto the polymer using standard techniques to form the bioadhesive material. An example of the grafting procedure is schematically depicted in Reaction 1, which depicts a nucleophilic substitution reaction between the amino group in the aromatic compound and the polymer. L-DOPA is grafted to maleic anhydride copolymers by reacting the free amine in L-DOPA with the maleic anhydride bond in the copolymer.

A variety of different polymers can be used as the backbone of the bioadhesive material. Representative polymers include 1:1 random copolymers of maleic anhydride with ethylene, vinyl acetate, styrene, or butadiene. The variable portions of the backbone structures are designated as the R groups at the bottom of Reaction 1. In addition, a number of other compounds containing aromatic rings with hydroxy substituents, such as tyrosine

or derivatives of catechol, can be used in reaction 1.

**Reaction 1**




**b. Polymer Synthesis**

In another embodiment, the polymers are prepared by conjugate addition of a compound containing an aromatic group and an amine functionality to one or more monomers containing an amino reactive group. In the preferred method the monomer is an acrylate or a polymer acrylate. In the most preferred method the monomer is a diacrylate such as 1,4-butanediol diacrylate; 1,3-propanediol diacrylate; 1,2-ethanediol diacrylate; 1,6-hexanediol diacrylate; 2,5-hexanediol diacrylate; or 1,3-propanediol diacrylate. In the coupling reaction, the monomer and the compound containing an aromatic group are each dissolved in an organic solvent (*e.g.*, THF, CH2Cl2, methanol, ethanol, CHCl3, hexanes, toluene, benzene, CCl4, glyme, diethyl ether, etc.) to form two solutions. The resulting solutions are combined, and the reaction mixture is heated to yield the desired polymer. The molecular weight of the synthesized polymer may be determined by the reaction conditions (*e.g.*, temperature, starting materials, concentration, solvent, etc) used in the synthesis.

For example, a monomer, such as 1,4 phenylene diacrylate or 1,4 butanediol

diacrylate having a concentration of 1.6 M, and DOPA or another primary amine containing aromatic molecule are each dissolved in an aprotic solvent such as DMF or DMSO to form two solutions, the solutions are mixed in a 1:1 molar ratio between the diacrylate and the amine group and heated to 56 °C to form a bioadhesive material.

**c. Blending a Polymer with a Catechol or Catechol Derivative**

Blends of a biodegradable or non-degradable polymer with a catechol or catechol derivative can be prepared by mixing, such as by dissolving the polymer and the catechol or catechol derivative in a suitable solvent and then removing the solvent under controlled conditions of temperature and rate of solvent removal. The resulting blends can be spray dried or dried at room temperature. Alternatively, the blend can be prepared by melt blending the polymer and the catechol or catechol derivative at a temperature corresponding to the melting point of the polymer. For example, polycaprolactone can be melt-blended with L-DOPA (m.p. 295°C) at a temperature of 58-60°C, which corresponds to the meting point of polycaprolactone. The blends can be also coated onto a substrate using melt extrusion, a fluidized bed, or any method of coating known in the art. The catechol or catechol derivative is present in amount from about 0.5% to about 95% by weight of the polymer.

**III. Method for Stabilizing Bioadhesives**

The invention includes a bioadhesive material comprising (1) a polymeric component selected from (a) a polymeric backbone and a side chain or side group containing an aromatic group substituted with one or more hydroxyl groups and (b) a polymer blended with an aromatic compound substituted with one or more hydroxyl groups and (2) an additive that stabilizes the polymeric component from erosion, dissolution or both, where at least 50% by weight of a 1 mm thick film of the bioadhesive material remains after 12 hours in a buffered pH 4.5 dissolution bath.

In certain embodiments, the bioadhesive material film is tested in a dissolution bath for 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 24 hours or longer. In certain such embodiments, the amount of bioadhesive material film remaining after testing in the dissolution bath is at least 50% by weight, at least 60% by weight, at least 70% by weight, at least 80% by weight, at least 90% by weight, at least 95% by weight, at least 97% by weight, at least 98% by weight or even at least 99% by weight. A suitable dissolution bath, a USP II apparatus, is described below in the Examples. In certain embodiments, the dissolution bath is stirred at 50 rpm and the temperature is 37° C.

In certain embodiments, the bioadhesive polymers are stabilized against erosion by incorporating one or more additives selected from (1) polyanhydrides, such as those having a molecular weight average in excess of 20,000, (2) acidic components (including precursors thereof), (3) metal compounds, (4) stabilizing polymers, and (5) hydrophobic components.

**a. Polyanhydrides**

Suitable polyanhydrides for stabilizing the bioadhesive polymers discussed above are described in U.S. Patent No. 4,757,128 to Domb et al. and U.S. Patent No. 5,955,096 to Mathiowitz et al., the contents of which are incorporated herein by reference. Polymers may be synthesized from highly pure isolated prepolymers formed from: aliphatic dicarboxylic acids, aromatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, combinations of aromatic, aliphatic and aromatic-aliphatic dicarboxylic acids, aromatic and aliphatic heterocyclic dicarboxylic acids and aromatic and aliphatic heterocyclic dicarboxylic acids in combination with aliphatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, and aromatic dicarboxylic acids of more than one phenyl group. For example, the following monomers are suitable for synthesizing bioadhesive copolymers: bis(p-carboxyphenoxy)alkanes; hydroquinone-O,O' diacetic acid; 1,4-bis-carboxymethyl benzene; 2,2-bis(4-hydroxphenyl)propane-O,O'-diacetic acid; 2,2-bis(4-carboxyphenyl)propane; terephthalic acid; bis(4-carboxyphenyl)alkanes; 1,4phenylene dipropionic acid; cyclohexane dicarboxylic acids, adipic acid, sebacic acid (SA), bis(p-carboxyphenoxy)propane (CPP), isophthalic acid (IPh), and dodecanedioic acid (DD). A particular polyanhydride is poly(fumaric acid-co-sebacic acid) (pFA:SA) (*e.g.* a 20:80 copolymer of p(FA:SA)). Another particular polyanhydride is polyadipic anhydride.

Anhydride monomers or oligomers can be incorporated into the polyanhydrides described above to enhance their bioadhesiveness. As used herein, the term "anhydride oligomer" refers to a diacid or polydiacid linked by anhydride bonds, and having carboxy end groups linked to a monoacid such as acetic acid by anhydride bonds. The anhydride oligomers have a molecular weight less than about 5000, typically between about 100 and 5000 daltons, or are defined as including between one to about 20 diacid units linked by anhydride bonds. The anhydride oligomer is hydrolytically labile. As analyzed by gel permeation chromatography, the molecular weight may be, for example, on the order of 200-400 for fumaric acid oligomer (FAPP) and 2000-4000 for sebacic acid oligomer (SAPP). In one embodiment, the diacids are those normally found in the Krebs glycolysis

cycle. The anhydride oligomer compounds preferably have high chemical reactivity. The anhydride oligomers may be combined with metal oxide particles to improve bioadhesion even more than with the organic additives alone.

Anhydride oligomers can be incorporated into a polyanhydride by combining a finely ground dispersion of particles of oligomer in a solution or dispersion with the polyanhydride. Alternatively, the oligomer compound can be incorporated into the polymer by dispersing the polyanhydride in a solution or dispersion of the oligomer compound and then removing the solvent by evaporation or filtration.

While Applicants do not wish to be bound by theory, it is believed that free carboxylic acid groups of the polyanhydrides form hydrogen bonds with hydroxyl group in the polymers functionalized or blended with catechol and derivatives thereof and/or create a local acidic environment, thereby stabilizing the latter polymers. It is also believed that the erosion of polyanhydrides is less affected by pH than the polymers functionalized or blended with catechol or a derivative, such that a polyanhydride selected for use herein advantageously erodes at a largely pH-independent rate and/or erodes slowly upon hydration.

Typically, the amount of polyanhydride added to a bioadhesive polymer is from about 0.5% to about 75% by weight, preferably about 5% to about 50% and more preferably about 10% to about 25%.

**b. Acidic Components**

The bioadhesive polymers can additionally be stabilized by the incorporation of a small molecule (*i.e.*, non-polymeric or oligomeric) acidic component, preferably a slow release acidic component. Typically, the acid is a weak organic acid, for example, an acid having a pKa of about 1 to about 7, such as about 1 to about 5.5, typically about 1.2 to 4.5. Preferably, the acid is poorly soluble in water as defined in the USP, but miscible with the bioadhesive polymer. The acid may contain one or more carboxylic, phosphonic, phosphoric, sulfonic, sulfinic or sulfenic acid moieties, preferably two or more acid moieties. Typically, the acid contains two or more carboxylic acid moieties. Exemplary acids include succinic acid, fumaric acid, citric acid, sebacic acid, adipic acid, lactic acid, malic acid, ascorbic acid, tartaric acid and sorbic acid. In certain embodiments, the acid is not citric acid. In certain such embodiments, the acid is not citric acid, fumaric acid, sebacic acid or lactic acid. In other embodiments, the acid is not a sugar. A combination of two or more such acids may be incorporated into a polymer.

The acid may be an acid precursor, particularly an anhydride. An acid precursor is a molecule that is hydrolyzed or metabolized into an acid. Suitable anhydrides includes symmetrical anhydrides (*e.g.*, acetic anhydride, cyclohexanecarboxylic anhydride, hexanoic anhydride, chloroacetic anhydride, thiobenzoic anhydride, thiopropionic anhydride, 2-chloroethanesulfinic anhydride, benzenesulfonic anhydride and cyclic anhydrides formed from two acid groups attached to the same molecule such as succinic anhydride, cyclohexane-1,2,3,4-tetracarboxylic acid 3,4-anhydride and phthalic anhydride), unsymmetric (mixed anhydrides (*e.g.*, acetic propionic anhydride, benzoic thioacetic anhydride, acetic chloroacetic anhydride, benzenesulfinic ethanesulfonic anhydride, chloroacetic-4-nitrobenzenesulfonic anhydride) and chalcogen analogues of anhydrides (*e.g.*, benzoic thioanhydride, 4-chlorocyclohexane-1-carbothioic thioanhydride, acetic propionic thioanhydride, acetic thiopropionic anhydride, propionic thioacetic anhydride, acetic thiopropionic thioanhydride, propionic thioacetic thioanhydride, thioacetic thiopropionic anhydride). Preferably, the anhydride is succinic anhydride, phthalic anhydride, maleic anhydride, adipic anhydride, butyric anhydride, isobutyric anhydride, propionic anhydride or another carboxylic acid anhydride. More preferably, the anhydride is succinic anhydride.

The acids advantageously are present in a bioadhesive polymer for an extended period of time (*e.g.*, not washed away in an aqueous environment), which is typically achieved either by virtue of low water solubility or by virtue of coating the acids with an appropriate coating. Such acids are collectively referred to herein as slow-release acid components. Acids selected on the basis of solubility typically have a solubility in water of less than 10 mg/mL at pH 4.5 and below. Coatings for an acid are selected such that they do not appreciably dissolve at pH 4.5 or below or such that they coat the acid until the formulation (*i.e.*, polymer) into which the coated acid is incorporated has passed through the stomach (*e.g.*, an enteric coating).

Typically, the amount of an acidic component (including acid precursors) added to a bioadhesive polymer is from about 0.5% to about 75% by weight, such as about 1% to about 65%, preferably about 5% to about 50% (about 5% to about 45%, about 10% to about 30%) and more preferably about 10% to about 25%.

**c. Metal Compounds**

The bioadhesive polymers described above can also be stabilized by the incorporation of a metal compound, as described in U.S. Patent No. 5,985,312 to Jacob et

al.

The metal compounds preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and hydroxides, including oxides of calcium, iron, copper and zinc. The metal compounds can be combined with a wide range of hydrophilic and hydrophobic polymers including proteins, polysaccharides and synthetic biocompatible polymers.

Metal compounds which can be incorporated into polymers preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and metal hydroxides, which are capable of becoming combined with a polymer to thereby improve the bioadhesiveness of the polymer. As defined herein, a water-insoluble metal compound is defined as a metal compound with little or no solubility in water, for example, less than about 0.0 to 0.9 mg/ml.

The water-insoluble metal compounds can be derived from a wide variety of metals, including, but not limited to, calcium, iron, copper, zinc, cadmium, zirconium and titanium. The water insoluble metal compound preferably is a metal oxide or hydroxide. Water insoluble metal compounds of multivalent metals are preferred. Representative metal oxides suitable for use in the compositions described herein include cobalt oxide (I) (CoO), cobalt oxide (II)($Co_2O_3$), selenium oxide ($SeO_2$), chromium double oxide ($CrO_2$), manganese oxide ($MnO_2$), titanium oxide ($TiO_2$), lanthanum oxide ($La_2O_3$), zirconium oxide ($ZrO_2$), silicon oxide ($SiO_2$), scandium oxide ($Sc_2O_3$), beryllium oxide (BeO), tantalum oxide ($Ta_2O_5$), cerium oxide ($CeO_2$), neodymium oxide ($Nd_2O_3$), vanadium oxide ($V_2O_5$), molybdenum oxide ($Mo_2O_3$), tungsten oxide (WO), tungsten trioxide ($WO_3$), samarium oxide ($Sm_2O_3$), europium oxide ($Eu_2O_3$), gadolinium oxide ($Gd_2O_3$), terbium oxide ($Tb_4O_7$), dysprosium oxide ($Dy_2O_3$), holmium oxide ($Ho_2O_3$), erbium oxide ($Er_2O_3$), thulium oxide ($Tm_2O_3$), ytterbium oxide ($Yb_2O_3$), lutetium oxide ($Lu_2O_3$), aluminum oxide ($Al_2O_3$), indium oxide ($InO_3$), germanium oxide ($GeO_2$), antimony oxide ($Sb_2O_3$), tellurium oxide ($TeO_2$), nickel oxide (NiO), and zinc oxide (ZnO). Other oxides include barium oxide (BaO), calcium oxide (CaO), nickel oxide (III) ($Ni_2O_3$), magnesium oxide (MgO), iron oxide (II) (FeO), iron oxide (III) ($Fe_2O_3$), copper oxide (II) (CuO), cadmium oxide (CdO), and zirconium oxide ($ZrO_2$). In certain embodiments, the metal compound is ferric oxide, copper oxide or zinc oxide or a combination thereof. In other embodiments, the metal compound is a zirconate, such as magnesium zirconate or calcium zirconate. In yet other embodiments, the metal compound is a silicate, such as magnesium silicate (*e.g.*, a hydrated magnesium

silicate such as talc) or calcium silicate. Advantageously, metal compounds which are incorporated into polymers are metal compounds which are already approved by the FDA or an equivalent agency as either food or pharmaceutical additives, such as zinc oxide or talc.

The water-insoluble metal compounds can be incorporated into a polymer by, for example, one of the following mechanisms: (a) physical mixtures which result in entrapment of the metal compound; (b) ionic interaction between metal compound and polymer; (c) surface modification of the polymers which would result in exposed metal compound on the surface; and (d) coating techniques such as fluidized bed, pan coating, or any similar methods known to those skilled in the art, which produce a metal compound enriched layer on the surface of the device. In one embodiment, nanoparticles or microparticles of the water-insoluble metal compound are incorporated into the polymer, preferably as a uniform dispersion.

Fine metal oxide particles can be produced, for example, by micronizing a metal oxide by mortar and pestle treatment to produce particles ranging in size, for example from 10.0 to 300 nm. The metal oxide particles can be incorporated into a polymer, for example, by dissolving or dispersing the particles into a solution or dispersion of the polymer.

Metal compounds are optionally coated with a protective coating, such as an enteric coating or a rate controlling coating. Such coatings are selected in order to release the metal compound only when the system is exposed to gastric fluid or another targeted environment. Typically, the amount of a metal compound added to a bioadhesive polymer is from about 1% to about 65% by weight, preferably about 5% to about 45% and more preferably about 10% to about 30%.

**d. Stabilizing Polymers**

The bioadhesive polymers described above can also be stabilized by the incorporation of certain polymers, particularly a hydrophilic polymer (hydrogel) that forms a rigid gel at pH 4.5 and higher or a hydrophobic polymer. Preferably, a hydrogel has little or no swelling at pH 4.5 or less. One group of suitable polymers includes polymers with pendant hydroxyl, carboxylic acid, amine, amide and/or urea moieties (or, more generally, hydrogen bond donors and/or acceptors). Specific examples of stabilizing polymers include polyvinyl alcohol, polyacrylamide, polyacrylonitrile, polymethacrylic acid, polyacrylic acid (*e.g.*, Carbomer), alginate (*e.g.*, sodium alginate), chitin, chitosan, zein and shellac. Typically, the hydrogel is Carbomer or an alginate. In certain embodiments, the stabilizing polymer is not an alginate. In certain embodiments, the stabilizing polymer is not ethyl

cellulose, cellulose acetate, zein, modified zein, chitin, and/or chitosan.

Stabilizing polymers can be combined with a bioadhesive polymer by combining a finely ground dispersion of particles in a solution or dispersion with the bioadhesive polymer. Alternatively, the stabilizing polymer can be combined with the bioadhesive polymer by dispersing the bioadhesive polymer in a solution or dispersion of the hydrogel and then removing the solvent by evaporation or filtration.

Typically, the amount of a stabilizing polymer added to a bioadhesive polymer is from about 1% to about 90% by weight, preferably about 5% to about 70% and more preferably about 10% to about 50%.

**e. Hydrophobic Components**

The bioadhesive polymers described above can also be stabilized by combination with one or more hydrophobic components. Examples of hydrophobic small molecules include waxy materials (*e.g.*, carnauba wax, beeswax, Chinese wax, spermaceti, lanolin, bayberry wax, Candelilla wax, castor wax, esparto wax, Japan wax, jojoba oil, ouricury wax, rice bran wax, ceresin waxes, montan wax, ozocerite, peat waxes, paraffin wax, polyethylene waxes) and polyglycerol fatty acid esters.

Typically, the amount of a hydrophobic component added to a bioadhesive polymer is from about 1% to about 25% by weight, preferably about 2% to about 10%.

**f. Combinations of Additives**

The stability of bioadhesive polymers can also be enhanced by incorporating materials from two or more of the classes of materials described above. Thus, the invention includes combinations including: (1) a polyanhydride and an acidic component, (2) a polyanhydride and a metal compound, (3) a polyanhydride and a stabilizing polymer, (4) a polyanhydride and a hydrophobic component, (5) an acidic component and a metal compound, (6) an acidic component and a stabilizing polymer, (7) an acidic component and a hydrophobic component, (8) a metal compound and a stabilizing polymer, (9) a metal compound and a hydrophobic component, (10) a stabilizing polymer and a hydrophobic component, (11) a polyanhydride and an acidic component and a metal compound, (12) a polyanhydride and an acidic component and a stabilizing polymer, (13) a polyanhydride and an acidic component and a hydrophobic component, (14) a polyanhydride and a metal compound and a stabilizing polymer, (15) a polyanhydride and a metal compound and a hydrophobic component, (16) a polyanhydride and a stabilizing polymer and a hydrophobic component, (17) an acidic component and a metal compound and a stabilizing polymer, (18)

an acidic component and a metal compound and a hydrophobic component, (19) an acidic component and a stabilizing polymer and a hydrophobic component, (20) a metal compound and a stabilizing polymer and a hydrophobic component, (21) a polyanhydride and an acidic component and a metal compound and a stabilizing polymer, (22) a polyanhydride and an acidic component and a metal compound and a hydrophobic component, (23) a polyanhydride and a metal compound and a stabilizing polymer and a hydrophobic component, (24) an acidic component and a metal compound and a stabilizing polymer and a hydrophobic component and (25) at least one material from each of the five categories. In a one embodiment, a combination of an acidic component and a hydrophobic component are incorporated into a bioadhesive polymer, particularly citric acid and ethylcellulose.

The proportion of additives, when there is a combination of additives, typically falls within the ranges for the individual classes of additives disclosed above.

Bioadhesive materials described herein may be used in a wide variety of drug delivery, tissue engineering, and other medical and diagnostic applications. Bioadhesive materials may be formed into the subject microparticles, such as microspheres or microcapsules, or may be a coating on such microparticles. In the preferred embodiment, the material is applied as a coating to a solid oral dosage formulation, such as a tablet or gel-capsule or to multiparticulates. The coating may be applied by direct compression or by applying a solution containing the material to the tablets or gel-capsules. In one embodiment, the bioadhesive material is in the matrix of a tablet or other drug delivery device. Optionally, the tablet or drug delivery device contains a coating, such as a coating containing the bioadhesive material, another bioadhesive polymer, a rate-controlling coating or an enteric coating.

Bioadhesive materials used as coatings preferably do not appreciably swell upon hydration, such that they do not substantially inhibit or block movement (*e.g.*, of ingested food) through the gastrointestinal tract, as compared to the polymers disclosed by Duchene *et al.* Generally, polymers that do not appreciably swell upon hydration include one or more hydrophobic regions, such as a polymethylene region (*e.g.*, $(CH_2)_n$, where n is 4 or greater). The swelling of a polymer can be assessed by measuring the change in volume when the polymer is exposed to an aqueous solution. Polymers that do not appreciably swell upon hydration expand in volume by 50% or less when fully hydrated. Preferably, such polymers expand in volume by less than 25%, less than 20%, less than 15%, less than 10% or less than 5%. A polymer that does not appreciably swell upon hydration can be mixed with a

polymer that does swell (*e.g.*, Carbopol™, poly(acrylic acid), provided that the amount of swelling in the polymer does not substantially interfere with bioadhesiveness.

In one embodiment, the bioadhesive coating consists of two layers, an inner bioadhesive layer that does not substantially swell upon hydration and an outer bioadhesive layer that is readily hydratable and optionally bioerodable, such as one comprised of Carbopol™.

A tablet or a drug eluting device can have one or more coatings in addition to the bioadhesive coating. These coatings and their thickness can, for example, be used to control where in the gastrointestinal tract the bioadhesive coating becomes exposed. In one example, the additional coating prevents the bioadhesive coating from contacting the mouth or esophagus. In another example, the additional coating remains intact until reaching the small intestine.

Examples of coatings include methylmethacrylates, zein, modified zein, chitin, chitosan, cellulose acetate, cellulose phthalate, HPMC, sugars, enteric polymers, gelatin and shellac. Premature dissolution of a tablet in the mouth can be prevented with hydrophilic polymers such as HPMC or gelatin.

Coatings used in tablets of the invention, typically include a pore former, such that the coating is permeable to the drug.

Tablets, capsules and drug eluting devices of the invention can be coated by a wide variety of methods. Suitable methods include compression coating, coating in a fluidized bed or a pan, hot melt (extrusion) coating and enrobing. Such methods are well known to those skilled in the art.

The bioadhesive coating adheres to the mucosa in the aqueous environment of the gastrointestinal tract. As a result, the bioavailability of therapeutic agents is enhanced through increased residence time at the target absorption rate. In a preferred embodiment, the solid oral dosage form contains rate controlling agents, such as hydroxypropylmethyl cellulose (HPMC) and microcrystalline cellulose (MCC). Optionally, the drug may be in the form or microparticles or nanoparticles. In one embodiment, a tablet contains a core containing a nanoparticulate drug and enhancers in a central matrix of rate controlling agents, such as hydroxypropylmethyl cellulose (HPMC) and microcrystalline cellulose (MCC). The core is surrounded on its circumference by bioadhesive polymer (preferably DOPA-BMA polymer). Optionally, the final tablet is coated with an enteric coating, such as Eudragit L100-55, to prevent release of the drug until the tablet has moved to the small

intestine.

The bioadhesive materials may be used in or as a coating on prosthetics, such as dental prosthetics. The materials may be used as dental adhesives, or bone cements and glues. The materials are suitable for use in wound healing applications, such as synthetic skins, wound dressings, and skin plasters and films.

In order to alter the physical properties of bioadhesive materials, additional components can be added to a composition. Such components include bioadhesive modifiers, solvents, thermoplastic polymers and plasticizers.

Bioadhesive materials can be mixed with one or more plasticizers or thermoplastic polymers. Such agents typically increase the strength and/or reduce the brittleness of polymeric coatings. Plasticizers can be hydrophobic or hydrophilic. Examples of plasticizers include dibutyl sebacate, polyethylene glycol, triethyl citrate, dibutyl adipate, dibutyl fumarate, diethyl phthalate, ethylene oxide-propylene oxide block copolymers such as Pluronic™ F68 and di(sec-butyl) fumarate. Example of thermoplastic polymers include polyesters, poly(caprolactone), polylactide, poly(lactide-co- glycolide), methyl methacrylate (*e.g.*, EUDRAGIT™), cellulose and derivatives thereof such as ethyl cellulose, cellulose acetate and hydroxypropyl methyl cellulose (HPMC) and large molecular weight polyanhydrides. The plasticizers and/or thermoplastic polymers are mixed with a bioadhesive polymer to achieve the desired properties. Typically, the proportion of plasticizers and thermoplastic polymers, when present, is from 0.5% to 50% by weight.

Bioadhesive modifiers include both natural and synthetic bioadhesive modifiers, which can be swellable or non-swellable and gellable or non-gellable. Swellable modifiers include fluid-imbibing displacement polymers (osmopolymers), such as poly(alkylene oxide), hydrogels (CARBOPOL®), polyacrylamide, crosslinked poly(indene-co-maleic anhydride), poly(acrylic acid), polysaccharides and polyglucan.

Gellable or non-gellable modifiers include karaya gum, guar gum, okra gum, gum arabic, acacia gum, pectina gum, ghatti gum, tragacanth gum, xanthan gum, locust bean gum, psyllium seed gum, tamarind gum, destria gum, casein gum and other gums.

Natural bioadhesive modifiers include cellulose compounds (cellulose, ethylcellulose, methylcellulose, nitrocellulose, propylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, carboxymethylcellulose and hydroxypropylmethylcellulose, including alkyl and hydroxyalkyl derivatives), karaya gum, prolamines (zein, modified zein, chitin, chitosan), L-DOPA, benserazide, carbidopa, dopamine, 3-O-methyldopa and other L-

DOPA metabolites. In certain embodiments, the natural bioadhesive modifiers exclude L-DOPA and/or its metabolites.

The bioadhesive modifiers can, for example, be blended with the bioadhesive materials of the invention during the preparation of a pharmaceutical composition. For tablets, a bioadhesive modifier is generally blended with a bioadhesive material though dry or wet mixing prior to tablet preparation.

As disclosed in U.S. Patent Nos. 5,985,312, 6,123,965 and 6,368,586, the contents of which are incorporated herein by reference, bioadhesive polymers and compositions, such as those named above, having a metal compound combined therewith have a further improved ability to adhere to tissue surfaces, such as mucosal membranes. The metal compound combined with the polymer can be, for example, a water-insoluble metal oxide. The combination of metal compounds with a wide range of different polymers, even those that are not normally bioadhesive, improves their ability to adhere to tissue surfaces such as mucosal membranes.

Control of the rate that an active drug (*e.g.*, a sustained release or controlled delivery form of a drug) is introduced to a targeted delivery site and its residence time at the targeted delivery site (*e.g.*, site of absorption) is achieved, at least in part, by using excipients, such as polymeric excipients. The exact mechanism by which a polymer interacts with the mucosa or controls the delivery of the drug is at least partially dependent on the rate of polymer hydration and swelling, which is related to its molecular weight. Therefore, any process that significantly reduces the molecular weight of the polymer is likely to affect its ability to control the drug delivery. Oxidative degradation can lead to a loss in molecular weight for several polymers commonly used in controlled release applications (Waterman, K. C., et. al., Pharm. Dev. Technol., 2002, 1-32). In addition to a loss in molecular weight, such degradation in polymers can produce reactive impurities and end groups to compromise the chemical stability of drugs and also their effectiveness as a bioadhesive polymer or release controlling agent. An example of class of controlled release polymers that can degrade to compromise the drug release rate is the polyoxyethylenes, including poly(ethylene oxides) (Polyox™), poly(ethylene glycols), and poly(oxyethylene) alkyl ethers. The polyethylene oxide is usually treated by the manufacturer (Dow chemicals) with 100-1000 ppm of butylated hydroxy toluene (BHT) to reduce such degradation. While this antioxidant is quite effective, it is volatile and can be lost during any heating steps and therefore it is advisable to include an additional antioxidants to the formulation matrix to

retain the polymer behavior intact (Waterman, K. C., et. al., Pharm. Dev. Technol., 2002, 1-32).

Hence, it is advisable to incorporate some stabilizers, preferably antioxidants or chelating agents, to inhibit any impurity-related degradation of drugs. Antioxidants can reduce formation of peroxides, but may be less effective in eliminating of peroxides already present in a dosage form. Currently, the marketed form of bupropion hydrochloride is stabilized with an antioxidant like L-cysteine hydrochloride. In contrast, chelating agents such as citric acid, edetic acid, fumaric acid and malic acid are recommended for inhibition of any metal induced oxidation. Chelating agents are generally more effective when added during a granulation step or by coating particles using fluid bed technology, rather than simply during physical mixing. Suitable antioxidants and chelating agents are disclosed in U.S. Pat. No. 6,423,351, the contents of which are incorporated herein by reference, which discloses prevention of drug oxidation using a ferrous ion source. Other suitable antioxidants include vitamin E, vitamin C, butylated hydroxytoluene, and butylated hydroxyanisole.

The pH to which a polymer is exposed can play a significant role in the stabilization of the polymer to oxidation. It is in general more difficult to remove an electron from a polymer when it is positively charged. For this reason, stability against oxidation is often greater under low pH conditions, which promote protonation of polymers if protonation is possible. In the converse, higher pH conditions, which deprotonate a polymer, generally make a drug more susceptible to oxidation.

U.S. Pat. Nos. 5,358,970; 5,541,231; 5,731,000 and 5,763,493 to Ruff et al, the contents of which are incorporated herein by reference, describe a stabilized bupropion hydrochloride formulation having a stabilizer selected from group consisting of L-cysteine hydrochloride, glycine hydrochloride, malic acid, sodium metabisulfite, citric acid, tartaric acid, L-cystine dihydrochloride, ascorbic acid, and isoascorbic(erythorbic) acid. Such stabilizers are useful herein as antioxidants and/or chelating agents. U.S. Pat. No. 6,652,882 to Odidi et. al describes stabilization of drug by a saturated polyglycolised glyceride like Gelucire™, and such compounds are suitable for use in the present invention.

Other oxidation stabilization strategies for bupropion formulations, which are suitable for use herein, include the addition of inorganic acids like hydrochloric acid, phosphoric acid, nitric acid and sulfuric acid (U.S. Pat. No. 5,968,553, the contents of which are incorporated herein by reference); dicarboxylic acids like oxalic acid, succinic acid,

adipic acid, fumaric acid, benzoic acid and phthalic acid (U.S. Pat. Nos. 6,194,002; 6,221,917; 6,242,496; 6,482,987 and 6,652,882, the contents of which are incorporated herein by reference); sulfites like potassium metabisulfite and sodium bisulfite (U.S. Pat. No. 6,238,697, the contents of which are incorporated herein by reference); organic esters like L-ascorbic acid palmitate, tocopherol solution in alcohol, butylated hydroxy anisole, tocopherol or tocopherol , vitamin E succinate, vitamin E 700 acetate, and L-ascorbic acid G palmitate (U.S. Pat. No. 6,312,716, the contents of which are incorporated herein by reference). The use of acidified granules of microcrystalline cellulose (U.S. Pat. No. 6,153,223, the contents of which are incorporated herein by reference); salts of organic bases like creatinine hydrochloride, pyridoxine hydrochloride and thiamine hydrochloride and inorganic acid like potassium phosphate monobasic (U.S. Pat. No. 6,333,332, the contents of which are incorporated herein by reference) is also suitable for the present invention.

Typically, antioxidants used in the present invention are selected from ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, malic acid, propyl gallate, sodium bisulfite, sodium sulfite, sodium metabisulfite, potassium metabisulfite, potassium bisulfite, sodium thiosulfate, sodium formaldehyde sulfoxylate, L-ascorbic acid, D-ascorbic acid, acetylcysteine, cysteine, thioglycerol, thioglycollic acid, thiolactic acid, thiourea, dithiothreitol, dithioerythreitol, glutathione, nordihydroguaiaretic acid, tocopherol, fumaric acid and succinic acid.

The term "acidification" refers to any method of lowering the pH of the bioadhesive polymers either before or after combination with a compatible pharmaceutical drug. Preferably, acidification employs a pharmaceutically acceptable acid to lower pH. Suitable pharmaceutically acceptable acids are well known in the art and include, by way of example only, hydrochloric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, succinic acid, lactic acid, and the like.

Preferably, an antioxidant or a chelating agent is added to a bioadhesive polymer prior to formulating it with a drug. The antioxidant or chelating agent can be added as a dry material or during wet granulation or following the extrusion or annealing process.

Antioxidants (also sometimes referred to as free radical absorbers) self-sacrificially stabilize materials against free radicals (for example, free radicals generated from photooxidation as a result of exposure to sunlight). The antioxidant and the bioadhesive polymer are preferably maintained in sufficiently close proximity such that a synergistic

effect on stability of polymer is achieved. In that regard, a a bioadhesive polymer (*e.g.*, a carbidopa-BMA polymer) can be maintained in sufficiently close proximity to the antioxidant moiety to enhance the stability of the polymer in an environment in which photo-oxidation can occur. Such close proximity is not typically obtained upon mere physical mixing of antioxidant and UV-absorber.

In order to further protect a drug formulation, an antioxidant can be present in combination with a UV-absorber such as PABA or BHT. These components can be localized such that the UV-absorber is within a single molecule (for example, within a single oligomeric or polymer chain). For example, the antioxidant and the UV-absorber can be localized through covalent bonding by reacting (for example, copolymerizing) at least one monomer including or incorporating the antioxidant with at least one monomer including or incorporating the UV-absorber. Antioxidants and UV-absorbers can also be conjugated to a suitably reactive polymer.

Antioxidants, chelating agents and UV-absorbers should be selected such that they do not react with a drug planned to be delivered with the polymer.

Typically, about 0.1% to about 20% by weight, such as about 0.5% to about 10% or about 1% to about 5%, of antioxidant and/or chelating agent is added to a bioadhesive polymer.

In general, there is no specific limitation on the material that can be encapsulated within the bioadhesive materials. Any kind of therapeutic, prophylactic or diagnostic agent, including organic compounds, inorganic compounds, proteins, polysaccharides, nucleic acids, or other materials can be incorporated using standard techniques. Flavorants, nutraceuticals, and dietary supplements are among the materials that can be incorporated in the bioadhesive material. In one embodiment, L-3,4-dihydroxyphenylalanine ("levodopa" or "L-dopa") is incorporated into the bioadhesive material for delivery to a patient. The bioadhesive material may contain carbidopa. In one embodiment, levodopa and carbidopa are both incorporated in the bioadhesive material. In a preferred embodiment, the bioadhesive material is a coating on an oral dosage formulation which contains levodopa and carbidopa in separate drug layers.

The bioadhesive polymer may also be used as one or more layers in a subject bioadhesive drug delivery tablet formulation.

*Polymer-Metal Complexes*

As described above, metal can be used to stabilize certain polymers. In addition, as

disclosed in U.S. Patent Nos. 5,985,312, 6,123,965 and 6,368,586 (the contents of which are incorporated herein by reference), polymers, such as those named above, having a metal compound incorporated therein have a further improved ability to adhere to tissue surfaces, such as mucosal membranes.

The metal compound incorporated into the polymer can be, for example, a water-insoluble metal oxide. The incorporation of metal compounds into a wide range of different polymers, even those that are not normally bioadhesive, improves their ability to adhere to tissue surfaces such as mucosal membranes.

The metal compounds preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and hydroxides, including oxides of calcium, iron, copper and zinc. The metal compounds can be combined with a wide range of hydrophilic and hydrophobic polymers including proteins, polysaccharides and synthetic biocompatible polymers.

Metal compounds which can be incorporated into polymers preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and metal hydroxides, which are capable of becoming combined with a polymer to thereby improve the bioadhesiveness of the polymer. As defined herein, a water-insoluble metal compound is defined as a metal compound with little or no solubility in water, for example, less than about 0.0 to 0.9 mg/ml.

The water-insoluble metal compounds can be derived from a wide variety of metals, including, but not limited to, calcium, iron, copper, zinc, cadmium, zirconium and titanium. The water insoluble metal compound preferably is a metal oxide or hydroxide. Water insoluble metal compounds of multivalent metals are preferred. Representative metal oxides suitable for use in the compositions described herein include cobalt oxide (I) (CoO), cobalt oxide (II)($Co_2O_3$), selenium oxide ($SeO_2$), chromium double oxide ($CrO_2$), manganese oxide ($MnO_2$), titanium oxide ($TiO_2$), lanthanum oxide ($La_2O_3$), zirconium oxide ($ZrO_2$), silicon oxide ($SiO_2$), scandium oxide ($Sc_2O_3$), beryllium oxide (BeO), tantalum oxide ($Ta_2O_5$), cerium oxide ($CeO_2$), neodymium oxide ($Nd_2O_3$), vanadium oxide ($V_2O_5$), molybdenum oxide ($Mo_2O_3$), tungsten oxide (WO), tungsten trioxide ($WO_3$), samarium oxide ($Sm_2O_3$), europium oxide ($Eu_2O_3$), gadolinium oxide ($Gd_2O_3$), terbium oxide ($Tb_4O_7$), dysprosium oxide ($Dy_2O_3$), holmium oxide ($Ho_2O_3$), erbium oxide ($Er_2O_3$), thulium oxide ($Tm_2O_3$), ytterbium oxide ($Yb_2O_3$), lutetium oxide ($Lu_2O_3$), aluminum oxide ($Al_2O_3$), indium oxide ($InO_3$), germanium oxide ($GeO_2$), antimony oxide ($Sb_2O_3$), tellurium oxide ($TeO_2$), nickel

oxide (NiO), and zinc oxide (ZnO). Other oxides include barium oxide (BaO), calcium oxide (CaO), nickel oxide (III) ($Ni_2O_3$), magnesium oxide (MgO), iron oxide (II) (FeO), iron oxide (III) ($Fe_2O_3$), copper oxide (II) (CuO), cadmium oxide (CdO), and zirconium oxide ($ZrO_2$).

In certain embodiments, the metal compound is ferric oxide, copper oxide or zinc oxide or a combination thereof. In other embodiments, the metal compound is a zirconate, such as magnesium zirconate or calcium zirconate. In yet other embodiments, the metal compound is a silicate, such as magnesium silicate (*e.g.*, a hydrated magnesium silicate such as talc) or calcium silicate. Advantageously, metal compounds which are incorporated into polymers are metal compounds which are already approved by the FDA or an equivalent agency as either food or pharmaceutical additives, such as zinc oxide or talc.

Preferred properties defining the metal compound include: (a) substantial insolubility in aqueous environments, such as acidic or basic aqueous environments (such as those present in the gastric lumen); and (b) ionizable surface charge at the pH of the aqueous environment.

The water-insoluble metal compounds can be incorporated into a polymer by, for example, one of the following mechanisms: (a) physical mixtures which result in entrapment of the metal compound; (b) ionic interaction between metal compound and polymer; (c) surface modification of the polymers which would result in exposed metal compound on the surface; and (d) coating techniques such as fluidized bed, pan coating, or any similar methods known to those skilled in the art, which produce a metal compound enriched layer on the surface of the device. In one embodiment, nanoparticles or microparticles of the water-insoluble metal compound are incorporated into the polymer, preferably as a uniform dispersion.

In one embodiment, the metal compound is provided as a fine particulate dispersion of a water-insoluble metal oxide which is incorporated throughout the polymer or at least on the surface of the polymer which is to be adhered to a tissue surface. The metal compound also can be incorporated in an inner layer of the polymer and exposed only after degradation or else dissolution of a "protective" outer layer. For example, a tablet core containing a polymer and metal may be covered with an enteric coating designed to dissolve when exposed to gastric fluid. The metal compound-enriched core then is exposed and become available for binding to GI mucosa.

Fine metal oxide particles can be produced, for example, by micronizing a metal oxide by mortar and pestle treatment to produce particles ranging in size, for example from 10.0 to 300 nm. The metal oxide particles can be incorporated into a polymer, for example, by dissolving or dispersing the particles into a solution or dispersion of the polymer.

Metal compounds are optionally coated with a protective coating, such as an enteric coating or a rate controlling coating. Such coatings are selected in order to release the metal compound only when the system is exposed to gastric fluid or another targeted environment.

Typically, the amount of a metal compound added to a bioadhesive polymer is from about 1% to about 65% by weight, preferably about 5% to about 45% and more preferably about 10% to about 30%.

Advantageously, metal compounds which are incorporated into polymers to improve their bioadhesive properties can be metal compounds which are already approved by the FDA as either food or pharmaceutical additives, such as zinc oxide.

Suitable polymers which can be used and into which the metal compounds can be incorporated include soluble and water-insoluble, and biodegradable and nonbiodegradable polymers, including hydrogels, thermoplastics, and homopolymers, copolymers and blends of natural and synthetic polymers, provided that they have the requisite fracture strength when mixed with a metal compound. In additional to those listed above, representative polymers which can be used in conjunction with a metal compound include hydrophilic polymers, such as those containing carboxylic groups, including polyacrylic acid. Bioerodible polymers including polyanhydrides, poly(hydroxy acids) and polyesters, as well as blends and copolymers thereof also can be used. Representative bioerodible poly(hydroxy acids) and copolymers thereof which can be used include poly(lactic acid), poly(glycolic acid), poly(hydroxy-butyric acid), poly(hydroxyvaleric acid), poly(caprolactone), poly(lactide-co-caprolactone), and poly(lactide-co-glycolide). Polymers containing labile bonds, such as polyanhydrides and polyorthoesters, can be used optionally in a modified form with reduced hydrolytic reactivity. Positively charged hydrogels, such as chitosan, and thermoplastic polymers, such as polystyrene also can be used.

Representative natural polymers which also can be used include proteins, such as zein, modified zein, chitin, chitosan, casein, gelatin, gluten, serum albumin, or collagen, and polysaccharides such as dextrans, polyhyaluronic acid and alginic acid. Representative synthetic polymers include polyphosphazenes, polyamides, polycarbonates,

polyacrylamides, polysiloxanes, polyurethanes and copolymers thereof. Celluloses also can be used. As defined herein the term "celluloses" includes naturally occurring and synthetic celluloses, such as alkyl celluloses, cellulose ethers, cellulose esters, hydroxyalkyl celluloses and nitrocelluloses. Exemplary celluloses include ethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate and cellulose sulfate sodium salt.

Polymers of acrylic and methacrylic acids or esters and copolymers thereof can be used. Representative polymers which can be used include poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

Other polymers which can be used include polyalkylenes such as polyethylene and polypropylene; polyarylalkylenes such as polystyrene; poly(alkylene glycols), such as poly(ethylene glycol); poly(alkylene oxides), such as poly(ethylene oxide); and poly(alkylene terephthalates), such as poly(ethylene terephthalate). Additionally, polyvinyl polymers can be used, which, as defined herein includes polyvinyl alcohols, polyvinyl ethers, polyvinyl esters and polyvinyl halides. Exemplary polyvinyl polymers include poly(vinyl acetate), polyvinyl phenol and polyvinylpyrrolidone.

Water soluble polymers can also be used. Representative examples of suitable water soluble polymers include polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and polyethylene glycol, copolymers of acrylic and methacrylic acid esters, and mixtures thereof. Water insoluble polymers also can be used. Representative examples of suitable water insoluble polymers include ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density,

poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethanes, and mixtures thereof. In one embodiment, a water insoluble polymer and a water soluble polymer are used together, such as in a mixture. Such mixtures are useful in controlled drug release formulations, wherein the release rate can be controlled by varying the ratio of water soluble polymer to water insoluble polymer.

Polymers varying in viscosity as a function of temperature or shear or other physical forces also may be used. Poly(oxyalkylene) polymers and copolymers such as poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO) or poly(ethylene oxide)-poly(butylene oxide) (PEO-PBO) copolymers, and copolymers and blends of these polymers with polymers such as poly(alpha-hydroxy acids), including but not limited to lactic, glycolic and hydroxybutyic acids, polycaprolactones, and polyvalerolactones, can be synthesized or commercially obtained. For example, polyoxyalkylene copolymers are described in U.S. Patent Nos. 3,829,506, 3,535,307, 3,036,118, 2,979,578, 2,677,700 and 2,675,619. Polyoxyalkylene copolymers are sold, for example, by BASF under the trade name PLURONICS™. These materials are applied as viscous solutions at room temperature or lower which solidify at the higher body temperature. Other materials with this behavior are known in the art, and can be utilized as described herein. These include KLUCEL™ (hydroxypropyl cellulose), and purified konjac glucomannan gum.

Other suitable polymers are polymeric lacquer substances based on acrylates and/or methacrylates, commonly called EUDRAGIT™ polymers (sold by Rohm America, Inc.). Specific EUDRAGIT™ polymers can be selected having various permeability and water solubility, which properties can be pH dependent or pH independent. For example, EUDRAGIT™ RL and EUDRAGIT™ RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, which are present as salts and give rise to the permeability of the lacquer films, whereas EUDRAGIT™ RL is freely permeable and EUDRAGIT™ RS is slightly permeable, independent of pH. In contrast, the permeability of EUDRAGIT™ L is pH dependent. EUDRAGIT™ L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water, but becomes increasingly soluble in a neutral to weakly alkaline solution by forming salts with alkalis. Above pH 5.0, the polymer becomes increasingly permeable.

Polymer solutions that are liquid at an elevated temperature but solid or gelled at

body temperature can also be utilized. A variety of thermoreversible polymers are known, including natural gel-forming materials such as agarose, agar, furcellaran, beta-carrageenan, beta-1,3-glucans such as curdlan, gelatin, or polyoxyalkylene containing compounds, as described above. Specific examples include thermosetting biodegradable polymers for *in vivo* use described in U.S. Patent No. 4,938,763, the contents of which are incorporated herein by reference.

*Polymer Blends with Monomers and/or Oligomers*

Polymers with enhanced bioadhesive properties are provided by incorporating anhydride monomers or oligomers into one of the polymers listed above by dissolving, dispersing, or blending, as taught by U.S. Patent Nos. 5,955,096 and 6,156,348, the contents of which are incorporated herein by reference. The polymers may be used to form drug delivery systems which have improved ability to adhere to tissue surfaces, such as mucosal membranes. The anhydride oligomers are formed from organic diacid monomers, preferably the diacids normally found in the Krebs glycolysis cycle. Anhydride oligomers which enhance the bioadhesive properties of a polymer have a molecular weight of about 5000 or less, typically between about 100 and 5000 daltons, or include 20 or fewer diacid units linked by anhydride linkages and terminating in an anhydride linkage with a carboxylic acid monomer.

The oligomer excipients can be blended or incorporated into a wide range of hydrophilic and hydrophobic polymers including proteins, polysaccharides and synthetic biocompatible polymers, including those described above. In one embodiment, anhydride oligomers may be combined with metal oxide particles, such as those described above, to improve bioadhesion even more than with the organic additives alone. Organic dyes, because of their electronic charge and hydrophobicity or hydrophilicity, can either increase or decrease the bioadhesive properties of polymers when incorporated into the polymers.

As used herein, the term "anhydride oligomer" refers to a diacid or polydiacid linked by anhydride bonds, and having carboxy end groups linked to a monoacid such as acetic acid by anhydride bonds. The anhydride oligomers have a molecular weight less than about 5000, typically between about 100 and 5000 daltons, or are defined as including between one to about 20 diacid units linked by anhydride bonds. In one embodiment, the diacids are those normally found in the Krebs glycolysis cycle. The anhydride oligomer compounds have high chemical reactivity.

The oligomers can be formed in a reflux reaction of the diacid with excess acetic

anhydride. The excess acetic anhydride is evaporated under vacuum, and the resulting oligomer, which is a mixture of species which include between about one to twenty diacid units linked by anhydride bonds, is purified by recrystallizing, for example, from toluene or other organic solvents. The oligomer is collected by filtration, and washed, for example, in ethers. The reaction produces anhydride oligomers of mono and poly acids with terminal carboxylic acid groups linked to each other by anhydride linkages.

The anhydride oligomer is hydrolytically labile. As analyzed by gel permeation chromatography, the molecular weight may be, for example, on the order of 200-400 for fumaric acid oligomer (FAPP) and 2000-4000 for sebacic acid oligomer (SAPP). The anhydride bonds can be detected by Fourier transform infrared spectroscopy by the characteristic double peak at 1750 $cm^{-1}$ and 1820 $cm^{-1}$, with a corresponding disappearance of the carboxylic acid peak normally at 1700 $cm^{-1}$.

In one embodiment, the oligomers may be made from diacids described for example in U.S. Patent Nos. 4,757,128, 4,997,904 and 5,175,235, the disclosures of which are incorporated herein by reference. For example, monomers such as sebacic acid, bis(p-carboxy-phenoxy)propane, isophathalic acid, fumaric acid, maleic acid, adipic acid or dodecanedioic acid may be used.

Organic dyes, because of their electronic charge and hydrophilicity or hydrophobicity, may alter the bioadhesive properties of a variety of polymers when incorporated into the polymer matrix or bound to the surface of the polymer. A partial listing of dyes that affect bioadhesive properties include, but are not limited to: acid fuchsin, alcian blue, alizarin red s, auramine o, azure a and b, Bismarck brown y, brilliant cresyl blue ald, brilliant green, carmine, cibacron blue 3GA, congo red, cresyl violet acetate, crystal violet, eosin b, eosin y, erythrosin b, fast green fcf, giemsa, hematoylin, indigo carmine, Janus green b, Jenner's stain, malachite green oxalate, methyl blue, methylene blue, methyl green, methyl violet 2b, neutral red, Nile blue a, orange II, orange G, orcein, paraosaniline chloride, phloxine b, pyronin b and y, reactive blue 4 and 72, reactive brown 10, reactive green 5 and 19, reactive red 120, reactive yellow 2,3, 13 and 86, rose bengal, safranin, Sudan III and IV, Sudan black B and toluidine blue.

*Polymers Functionalized with Hydroxy-Substituted Aromatic Groups*

Polymers having an aromatic group which contains one or more hydroxyl groups grafted onto them or coupled to individual monomers are also suitable for use in the bioadhesive coatings of the invention. Such polymers can be biodegradable or non-

biodegradable polymers. The polymer can be hydrophobic. Preferably, the aromatic group is catechol or a derivative thereof and the polymer contains reactive functional groups. Typically, the polymer is a polyanhydride and the aromatic compound is the catechol derivative DOPA. These materials display bioadhesive properties superior to conventional bioadhesives used in therapeutic and diagnostic applications.

The molecular weight of the suitable polymers and percent substitution of the polymer with the aromatic group may vary greatly. The degree of substitution varies based on the desired adhesive strength, it may be as low as 10%, 25% or 50%, or up to 100% substitution. Generally, at least 50% of the monomers in the polymeric backbone are substituted with at least one aromatic group. Preferably, about 100% of the monomers in the polymeric backbone are substituted with at least one aromatic group. The resulting polymer has a molecular weight ranging from about 1 to 2,000 kDa.

The polymer that forms that backbone of the bioadhesive material can be a biodegradable polymer. Examples of preferred biodegradable polymers include synthetic polymers such as poly hydroxy acids, such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyesters, polyurethanes, poly(butyric acid), poly(valeric acid), poly(caprolactone), poly(hydroxybutyrate), poly(lactide-co-glycolide) and poly(lactide-cocaprolactone), and natural polymers such as alginate and other polysaccharides, collagen and chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein, modified zein, chitin, chitosan, and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo* and by surface or bulk erosion. The foregoing materials may be used alone, as physical mixtures (blends), or as co-polymers.

Suitable polymers can formed by first coupling the aromatic compound to the monomer and then polymerizing. In this example, the monomers may be polymerized to form a polymer backbone, including biodegradable and non-biodegradable polymers. Suitable polymer backbones include, but are not limited to, polyanhydrides, polyamides, polycarbonates, polyalkylenes, polyalkylene oxides such as polyethylene glycol, polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyethylene, polypropylene, poly(vinyl acetate), poly(vinyl chloride), polystyrene, polyvinyl halides, polyvinylpyrrolidone, polyhydroxy

acids, polysiloxanes, polyurethanes and copolymers thereof, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitrocellulloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, and polyacrylates such as poly(methyl methacrylate), poly(ethylmethacrylate), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecylmethacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate).

A suitable polymer backbone can be a known bioadhesive polymer that is hydrophilic or hydrophobic. Hydrophilic polymers include CARBOPOL™, polycarbophil, cellulose esters, and dextran.

Non-biodegradable polymers, especially hydrophobic polymers are also suitable as polymer backbones. Examples of preferred non-biodegradable polymers include ethylene vinyl acetate, poly(methacrylic acid), copolymers of maleic anhydride with other unsaturated polymerizable monomers, poly(butadiene maleic anhydride), polyamides, copolymers and mixtures thereof and dextran, cellulose and derivatives thereof.

Hydrophobic polymer backbones include polyanhydrides, poly(ortho)esters, and polyesters such as polycaprolactone. Preferably, the polymer is sufficiently hydrophobic that it is not readily water soluble, for example the polymer should be soluble up to less than about 1% w/w in water, preferably about 0.1% w/w in water at room temperature or body temperature. In the most preferred embodiment, the polymer is a polyanhydride, such as a poly(butadiene maleic anhydride) or another copolymer of maleic anhydride.

Polyanhydrides may be formed from dicarboxylic acids as described in U.S. Patent No. 4,757,128 to Domb *et al.*, incorporated herein by reference. Suitable diacids include aliphatic dicarboxylic acids, aromatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acid, combinations of aromatic, aliphatic and aromatic-aliphatic dicarboxylic acids, aromatic and aliphatic heterocyclic dicarboxylic acids, and aromatic and aliphatic heterocyclic dicarboxylic acids in combination with aliphatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, and aromatic dicarboxylic acids of more than one phenyl group. Suitable monomers include sebacic acid (SA), fumaric acid (FA), bis(p-carboxyphenoxy)propane (UP), isophthalic acid (IPh), and dodecanedioic acid (DD).

A wide range of molecular weights are suitable for the polymer that forms the backbone of the bioadhesive material. The molecular weight may be as low as about 200 Da (for oligomers) up to about 2,000 kDa. Preferably the polymer has a molecular weight of at least 1,000 Da, more preferably at least 2,000 Da, most preferably the polymer has a molecular weight of up to 20 kDa or up to 200 kDa. The molecular weight of the polymer may be up to 2,000 kDa.

The range of substitution on the polymer varies greatly and depends on the polymer used and the desired bioadhesive strength. For example, a butadiene maleic anhydride copolymer that is 100% substituted with DOPA will have the same number of DOPA molecules per chain length as a 67% substituted ethylene maleic anhydride copolymer. Typically, the polymer has a percentage substitution ranging from 10% to 100%, preferably ranging from 50% to 100%.

The polymers and copolymers that form the backbone of the bioadhesive material include reactive functional groups that interact with the functional groups on the aromatic compound.

It is desirable that the polymer or monomer that forms the polymeric backbone contains accessible functional groups that easily react with molecules contained in the aromatic compounds, such as amines and thiols. In a preferred embodiment, the polymer contains amino reactive moieties, such as aldehydes, ketones, carboxylic acid derivatives, cyclic anhydrides, alkyl halides, aryl azides, isocyanates, isothiocyanates, succinimidyl esters or a combination thereof.

Preferably, the aromatic compound containing one or more hydroxyl groups is catechol or a derivative thereof. Optionally, the aromatic compound is a polyhydroxy aromatic compound, such as a trihydroxy aromatic compound (*e.g.*, phloroglucinol) or a multihydroxy aromatic compound (*e.g.*, tannin). The catechol derivative may contain a reactive group, such as an amino, thiol, or halide group. The preferred catechol derivative is 3,4-dihydroxyphenylalanine (DOPA), which contains a primary amine. Tyrosine, the immediate precursor of DOPA, which differs only by the absence of one hydroxyl group in the aromatic ring, can also be used. Tyrosine is capable of conversion (*e.g.*, by hydroxylation) to the DOPA form. A particularly preferred aromatic compound is an amine-containing aromatic compound, such as an amine-containing catechol derivative (*e.g.*, dopamine).

Two general methods are used to form the polymer product. In one example, a

compound containing an aromatic group which contains one or more hydroxyl groups is grafted onto a polymer. In this example, the polymeric backbone is a biodegradable polymer. In a second example, the aromatic compound is coupled to individual monomers and then polymerized.

Any chemistry which allows for the conjugation of a polymer or monomer to an aromatic compound containing one or more hydroxyl groups can be used, for example, if the aromatic compound contains an amino group and the monomer or polymer contains an amino reactive group, this modification to the polymer or monomer is performed through a nucleophilic addition or a nucleophilic substitution reaction, such as a Michael-type addition reaction, between the amino group in the aromatic compound and the polymer or monomer. Additionally, other procedures can be used in the coupling reaction. For example, carbodiimide and mixed anhydride based procedures form stable amide bonds between carboxylic acids or phosphates and amino groups, bifunctional aldehydes react with primary amino groups, bifunctional active esters react with primary amino groups, and divinylsulfone facilitates reactions with amino, thiol, or hydroxy groups.

The aromatic compounds are grafted onto the polymer using standard techniques to form the bioadhesive material. In one example, L-DOPA is grafted to maleic anhydride copolymers by reacting the free amine in L-DOPA with the maleic anhydride bond in the copolymer.

A variety of different polymers can be used as the backbone of the bioadhesive material, as described above. Additional representative polymers include 1:1 random copolymers of maleic anhydride with ethylene, vinyl acetate, styrene, or butadiene. In addition, a number of other compounds containing aromatic rings with hydroxy substituents, such as tyrosine or derivatives of catechol, can be used in this reaction.

In another embodiment, the polymers are prepared by conjugate addition of a compound containing an aromatic group that is attached to an amine to one or more monomers containing an amino reactive group. In a preferred method, the monomer is an acrylate or the polymer is acrylate. For example, the monomer can be a diacrylate such as 1,4-butanediol diacrylate, 1,3-propanediol diacrylate, 1,2-ethanediol diacrylate, 1,6-hexanediol diacrylate, 2,5-hexanediol diacrylate or 1,3-propanediol diacrylate. In an example of the coupling reaction, the monomer and the compound containing an aromatic group are each dissolved in an organic solvent (*e.g.*, THF, $CH_2Cl_2$, methanol, ethanol, $CHCl_3$, hexanes, toluene, benzene, $CCl_4$, glyme, diethyl ether, *etc.*) to form two solutions.

The resulting solutions are combined, and the reaction mixture is heated to yield the desired polymer. The molecular weight of the synthesized polymer can be controlled by the reaction conditions (*e.g.*, temperature, starting materials, concentration, solvent, *etc.*) used in the synthesis.

For example, a monomer, such as 1,4-phenylene diacrylate or 1,4-butanediol diacrylate having a concentration of 1.6 M, and DOPA or another primary amine containing aromatic molecule are each dissolved in an aprotic solvent such as DMF or DMSO to form two solutions. The solutions are mixed to obtain a 1:1 molar ratio between the diacrylate and the amine group and heated to 56 °C to form a bioadhesive material.

*Bioadhesive Polymer Blends*

Hydrophobic polymers, such as polyesters, poly (anhydrides), ethyl cellulose, even if possibly non-adhesive on their own, may nevertheless be made bioadhesive simply by physically mixing the hydrophobic polymers with one or more suitable compounds (such as catechols or derivatives L-DOPA, D-DOPA, dopamine, or carbidopa, *etc.*) to create "bioadhesive compositions." Similarly, metal oxides may also be used for this purpose.

The molecular weight of the bioadhesive polymers and percent substitution of the polymers with residues of the compounds disclosed may vary greatly. The degree of substitution varies based on the desired adhesive strength, it may be as low as 10%, 20%, 25%, 50%, or up to 100% substitution. On average, at least 50% of the repeat units in the polymeric backbone are substituted with at least one residue. In one particular embodiment, 75-95% of the residues in the backbone are substituted with at least one residue. In another particular embodiment, on average 100% of the repeat units in the polymeric backbone are substituted with at least one residue. The resulting bioadhesive polymer typically has a molecular weight ranging from about 1 to 2,000 kDa, such as 1 to 1,000 kDa, 10 to 1,000 kDa or 100 to 1,000 kDa. Polymers used in bioadhesive compositions typically have the same range of molecular weights.

Unlike the bioadhesive polymers described above, there is typically no covalent bond formed between the compounds and the polymer in the bioadhesive compositions (*i.e.*, the polymer does not chemically react with the compound, although hydrogen bonds, ionic bonds and/or van der Waals interactions can occur).

Suitable polymers for use in bioadhesive compositions are described above. Typically, the polymer itself may not be bioadhesive, but the polymer can be bioadhesive (*e.g.*, a polymer with hydrogen bond-forming pendant groups). Preferably, the polymer is a

hydrophobic polymer such as a poly(lactone), *e.g.*, poly(caprolactone).

To form the bioadhesive compositions of the invention, typically a polymer and a suitable compound are dissolved in a compatible solvent and mixed together. The solvent is then evaporated, preferably at a controlled temperature and rate of removal. Alternatively or in combination with general evaporation, the bioadhesive composition can be spray dried or dried at room temperature.

In another example, a mixture of a polymer and a suitable compound are melted at or slightly above the melting point of the polymer, typically while being mixed. Both the polymer and the suitable compound should be selected such that they are chemically stable (*e.g.*, do not decompose, do not become oxidized) at the melting point temperature. After the composition has re-solidified, it can be milled in order to obtain particles of the desired size.

The subject bioadhesive compositions can also be prepared by dry mixing of a polymer and a suitable compound, provided that the suitable compound is sufficiently distributed throughout the composition.

In each of the above methods, additional components can be added to the mixture prior to dissolution, melting and/or mixing. The additional components are preferably stable under the conditions the mixture is exposed to. In particular, active agents should be stable at the melting point temperature if that method is employed.

The weight ratio of polymer to the suitable compound in a bioadhesive composition can be selected to give the desired amount of bioadhesion. Typically, the weight ratio of polymer to compound is 9:1 to 1:9, such as 3:1 to 1:3 or 2:1 to 1:2. For example, when the polymer is predominant component, the weight ratio is 9:1 to 1:1, 3:1 to 1:1 or 2:1 to 1:1.

In the subject methods and pharmaceutical compositions, the suitable compounds (such as L-DOPA, D-DOPA, dopamine, or carbidopa, *etc.*) may be used as agents to render the hydrophobic polymers bioadhesive, and/or be used as active ingredients in the pharmaceutical composition to be delivered to the patient. Thus, in certain embodiments, if carbidopa is used as part of the bioadhesive layer (for example, as the bioadhesive material on the shell of Figure 5, or as the layer to coat the core comprising the second zero-order release portion), the total carbidopa dosage may be adjusted to account for the release of carbidopa from the bioadhesive material.

Similarly, in certain embodiments, when L- or D-dopa is used as the suitable compound to render the hydrophobic polymer bioadhesive, the dosage of total levodopa or

precursor thereof may be adjusted elsewhere in, for example, the relevant portion or sub-portions of the IR or CR (controlled release, *e.g.*, zero-order release rate portion).

In certain embodiments, a higher proportion of L-dopa (or D-Dopa) may be used to achieve a significant amount of release (*e.g.*, more or less immediate release) from the polymers. In other embodiments, less L- or D-Dopa may be used such that the polymer is still adhesive, but the release of L- or D-Dopa from the bioadhesive polymer is less significant compared to the levodopa or precursors thereof in IR, and/or one or more other portions or sub-portions of the subject dosage form.

Coatings

Preferred bioadhesive coatings do not appreciably swell upon hydration, such that they do not substantially inhibit or block movement (*e.g.*, of ingested food) through the gastrointestinal tract, as compared to the polymers disclosed by Duchene *et al.* Generally, polymers that do not appreciably swell upon hydration include one or more hydrophobic regions, such as a polymethylene region (*e.g.*, $(CH_2)_n$, where n is 4 or greater). The swelling of a polymer can be assessed by measuring the change in volume when the polymer is exposed to an aqueous solution. Polymers that do not appreciably swell upon hydration expand in volume by 50% or less when fully hydrated. Preferably, such polymers expand in volume by less than 25%, less than 20%, less than 15%, less than 10% or less than 5%. Even more preferably, the bioadhesive coatings are mucophilic. A polymer that does not appreciably swell upon hydration can be mixed with a polymer that does swell (*e.g.*, Carbopol™, poly(acrylic acid), provided that the amount of swelling in the polymer does not substantially interfere with bioadhesiveness.

In one embodiment, the bioadhesive polymeric coating has two layers, an inner bioadhesive layer that does not substantially swell upon hydration and an outer bioadhesive layer that is readily hydratable and optionally bioerodable, such as one comprised of Carbopol™.

The bioadhesive polymers discussed above can be mixed with one or more plasticizers or thermoplastic polymers. Such agents typically increase the strength and/or reduce the brittleness of polymeric coatings. Examples of plasticizers include dibutyl sebacate, polyethylene glycol, triethyl citrate, dibutyl adipate, dibutyl fumarate, diethyl phthalate, ethylene oxide-propylene oxide block copolymers such as Pluronic™ F68 and di(sec-butyl) fumarate. Example of thermoplastic polymers include polyesters, poly(caprolactone), polylactide, poly(lactide-co- glycolide), methyl methacrylate (*e.g.*,

EUDRAGIT™), cellulose and derivatives thereof such as ethyl cellulose, cellulose acetate and hydroxypropyl methyl cellulose (HPMC) and large molecular weight polyanhydrides. The plasticizers and/or thermoplastic polymers are mixed with a bioadhesive polymer to achieve the desired properties. Typically, the proportion of plasticizers and thermoplastic polymers, when present, is from 0.5% to 40% by weight.

In one embodiment, the bioadhesive polymer coating, in a dry packaged form of a tablet, is a hardened shell.

A tablet or a drug eluting device can have one or more coatings in addition to the bioadhesive polymeric coating. These coatings and their thickness can, for example, be used to control where in the gastrointestinal tract the bioadhesive coating becomes exposed. In one example, the additional coating prevents the bioadhesive coating from contacting the mouth or esophagus. In another example, the additional coating remains intact until reaching the small intestine (*e.g.*, an enteric coating).

Examples of coatings include methylmethacrylates, zein, modified zein, chitin, chitosan, cellulose acetate, cellulose phthalate, HMPC, sugars, enteric polymers, gelatin and shellac. Premature dissolution of a tablet in the mouth can be prevented with hydrophilic polymers such as HPMC or gelatin.

Coatings used in tablets of the invention typically include a pore former, such that the coating is permeable to the drug. Exemplary pore formers include: sugar, mannitol, HPC (hydroxypropyl cellulose), HPMC, dendrites, NaCl, *etc.*

Tablets and drug eluting devices of the invention can be coated by a wide variety of methods. Suitable methods include compression coating, coating in a fluidized bed or a pan, enrobing, and hot melt (extrusion) coating, *etc.* Such methods are well known to those skilled in the art.

All the above compositions, derivatives, precursors, additional components that can be used with levodopa / carbidopa, dosage forms, methods of making and using, *etc.*, are adaptable or directly useable with the instant invention, and are thus expressly incorporated herein by reference.

**Examples:**

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the

specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

Example 1 ***Release Profile of a Dosage Form with IR+CR+IR Componets***

Figures 15 and 16 show two representative release profiles of a subject dosage formulation comprising a first immediate release portion (IR), a second substantially zero-order release portion (CR), and a third portion comprising a second immediate release portion (IR).

Specifically, Figure 15 shows a representative release profile of an exemplary dosage formulation comprising a first immediate release portion (IR), a second substantially zero-order release portion (CR), and a third delayed immediate release portion (IR). For instance, each of the three portions may amount to about 1/3 of the total dosage form.

The percentage of carbidopa and levodopa released over time clearly shows a three-stage release profile. In the first stage of release, the first IR portion is rapidly dissolved, such that about 30% of the total carbidopa and about 30% of the total levodopa are released within about 30 minutes. Then both carbidopa and levodopa are released at a substantially zero-order release rate, such that another about 30-40% of the total carbidopa and another about 30-40% of the total levodopa are released over the next 3-4 hours. At the end of the second portion release, the third release stage (IR portion) began. During the third portion of release a final 30% of the total carbidopa and levodopa are dissolved within about 2-4 hours.

The ratio of levodopa-carbidopa in this exemplary dosage formulation is roughly the same (constant) in all three portions. But it needs not be the case in other embodiments of the invention. In addition, the release rate of carbidopa and levodopa from this exemplary dosage formulation is roughly the same. Again, this needs not be the case in other embodiments of the invention. Finally, the exemplary dosage formulation delivers carbidopa and levodopa at roughly the same time. This needs not be the case in other embodiments of the invention.

Figure 16 shows a representative release profile of an exemplary dosage formulation comprising a first immediate release portion (IR), a second substantially zero-order release portion (CR), and a third delayed immediate release portion (IR). For instance, each of the

three portions may amount to about 1/3 of the total dosage form.

The percentage of carbidopa and levodopa released over time clearly shows a three-stage release profile. In the first stage of release, the first IR portion is rapidly dissolved, such that about 30% of the total carbidopa and about 30% of the total levodopa are released within about 30 minutes. Then both carbidopa and levodopa are released at a substantially zero-order release rate, such that another about 30-40% of the total carbidopa and another about 30-40% of the total levodopa are released over the next 3-4 hours. At the end of the second portion release, the third release stage (IR portion) began. Again, the third portion release generates relatively steep lines representing carbidopa and levodopa dissolution, such that a final 30% of the total levodopa and carbidopa are dissolved within about 1-2 hours.

The ratio of levodopa-carbidopa in this exemplary dosage formulation is roughly the same (constant) in all three portions. But it needs not be the case in other embodiments of the invention. In addition, the release rate of levodopa and carbidopa from this exemplary dosage formulation is roughly the same. Again, this needs not be the case in other embodiments of the invention. Finally, the exemplary dosage formulation delivers levodopa and carbidopa at roughly the same time. This needs not be the case in other embodiments of the invention.

**Example 2** ***In vivo Release of Levodopa and Carbidopa***

The following experiment was designed to determine if effective levodopa concentration *in vivo* is increased at the presence of a higher ratio of carbidopa to levodopa (as compared to that used in conventional therapy).

SINEMET® CR tablets (50 mg carbidopa / 200 mg levodopa) were administered to fed beagle dogs either alone or after pre-dosing with 12.5 mg of carbidopa, and plasma concentrations of carbidopa and levodopa were measured over time (data not shown). The AUC (Area Under the Concentration-time curve) for each set of measurements were also summarized in Table 1 below.

Table I $AUC_{0\text{-}24}$ (ng/mL × hr) of Carbidopa and Levodopa

| | SINEMET® CR | Carbidopa + SINEMET® CR |
|---|---|---|
| Levodopa | 3903 ± 298 | 8640 ± 2064 |
| Carbidopa | 215 ± 43 | 592 ± 303 |

Table I clearly shows a significant (almost 100%) increase in both peak

concentrations for carbidopa and levodopa, and $AUC_{0-24}$, despite the fact that the total amount of levodopa in all experiments remained the same (*e.g.*, 200 mg). This demonstrates that higher ratio of carbidopa / levodopa in the immediate release portion, or pre-dosing using carbidopa can lead to a higher effective levodopa concentration or AUC in animal models.

**Example 3** ***Exemplary Multilayer Tablet and Multiparticulate Capsule Formulations***

Given any specific release profiles, the effective components of the subject pharmaceutical compositions may be formulated in a number of ways to achieve the given release profile. The following examples provide two specific formulations – a multilayer tablet form and a multiparticulate capsule form – that both may be formulated to achieve substantially the same release profile.

For both the tablet and the capsule forms, the subject pharmaceutical compositions (*e.g.*, Levodopa and/or Carbidopa) may be formulated as extended release formulations. Applicants have provided two different formulations, the multilayer tablet and the multiparticulate capsule forms. The multilayer extended release tablet approach is identical to the multiparticulate extended release capsule formulations with respect to the active pharmaceutical ingredients and the achieved dose level.

The SPHEROMER™ III or IV bioadhesive polymers, citric acid, and hydroxypropyl cellulose components are common to both the tablet formulation and the multiparticulate extended release capsule formulations. Additional excipients used in the multilayer extended release tablet formulations include magnesium stearate, succinic acid, hypromellose, corn starch, Ludipress®, butylated hydroxytoluene and p[FA:SA] or (SPHEROMER™ I). Poly[fumaric-co-sebacic acid anhydride] or p[FA:SA] (SPHEROMER™ I), is a bioadhesive polymer developed by Applicants that is similar to SPHEROMER™ III. All other excipients utilized in the multilayer extended release tablet formulations meet USP/NF specifications.

One exemplary multilayer extended release formulation approach provides a four-layer tablet. In this system, an immediate release (IR) active layer comprises levodopa/carbidopa, Ludipress®, citric acid, butylated hydroxytoluene and magnesium stearate. An inner controlled release (CR) layer is composed of levodopa, carbidopa, corn starch, succinic acid, butylated hydroxytoluene, magnesium stearate and hypromellose polymers. The CR layer is sandwiched between two bioadhesive layers containing

poly[fumaric-co-sebacic acid] or p[FA:SA], citric acid, and levodopa-(graft) butadiene maleic anhydride polymer (SPHEROMER™ III). Formulations A and B differ in the levels of rate-controlling hypromellose polymers in the inner CR layer and consequently have different dissolution profiles for levodopa and carbidopa.

Unit dose composition of Levodopa-Carbidopa Multilayer Extended Release Tablet Type A and Type B formulations are listed below in Table A and Table B, respectively.

**Table A:** Unit dose composition of Levodopa-Carbidopa Multilayer Extended Release Tablet, 200mg/50mg Type A

| Components | %w/w | Wt per Tablet (mg) |
|---|---|---|
| Levodopa, USP | 20.25 | 200.0 |
| Carbidopa, monohydrate, USP | 5.46 | 53.9 |
| Citric acid, anhydrous, USP | 2.49 | 24.6 |
| Succinic Acid, FCC | 6.58 | 65.0 |
| Butylated hydroxytoluene, NF | 0.04 | 0.4 |
| Hypromellose 2208, 100 cps, USP | 3.58 | 35.3 |
| Corn Starch, NF | 0.98 | 9.7 |
| Hypromellose 2910, 5 cps, USP | 5.32 | 52.5 |
| Ludipress® | 6.00 | 59.2 |
| Magnesium stearate, NF | 0.27 | 2.7 |
| SPHEROMER™ III | 31.53 | 311.3 |
| p[FA:SA] 1:4, (SPHEROMER™ I) | 10.93 | 107.9 |
| Hydroxypropylcellulose, NF | 6.57 | 64.9 |
| Dehydrated alcohol, USP | * | * |
| Methylene Chloride, NF | * | * |
| Methyl alcohol NF | * | * |
| **Total** | **100.00** | **987.4** |

* Evaporated during drying of granulation.

**Table B**: Unit dose composition of Levodopa-Carbidopa Multilayer Extended Release Tablet, 200mg/50mg Type B

| Components | %w/w | Wt per Tablet (mg) |
|---|---|---|
| Levodopa, USP | 20.25 | 200.0 |
| Carbidopa, monohydrate, USP | 5.46 | 53.9 |
| Citric acid, anhydrous, USP | 2.49 | 24.6 |
| Succinic Acid, FCC | 6.58 | 65.0 |
| Butylated hydroxytoluene, NF | 0.04 | 0.40 |
| Hypromellose 2208, 100 cps, USP | 7.13 | 70.3 |
| Hypromellose 2208, 4000 cps, USP | 0.35 | 3.5 |
| Corn Starch, NF | 0.63 | 6.2 |
| Hypromellose 2910, 5 cps, USP | 1.77 | 17.5 |
| Ludipress® | 6.00 | 59.2 |
| Magnesium stearate, NF | 0.27 | 2.7 |
| SPHEROMER™ III | 31.53 | 311.3 |
| p[FA:SA] 1:4 (SPHEROMER™ I) | 10.93 | 107.9 |
| Hydroxypropylcellulose, NF | 6.57 | 64.9 |
| Dehydrated alcohol, USP | * | * |
| Methylene Chloride, NF | * | * |
| Methyl alcohol, NF | * | * |
| **Total** | **100.00** | **987.4** |

* Evaporated during drying of granulation.

With the exception of SPHEROMER™ I, and SPHEROMER™ III, all excipients utilized in both formulations are within or below the listed levels for orally administered products.

The subject bioadhesive multilayer extended releases tablets using p[FA:SA] as the bioadhesive polymer typically result in an improved bioavailability and reduced variability compared to SINEMET® tablets. Such formulations and dosage forms can be generally used

for a broad spectrum of compounds (*e.g.*, drugs, prodrugs, metabolic precursors, *etc.*), especially those with limited absorption windows in upper GI (*e.g.*, stomach), such as levodopa and carbidopa.

Examples below provide details of making the various component pellets in the subject pharmaceutical compositions (such as levodopa, carbidopa, or levodopa-carbidopa pellets), the *in vitro* and/or *in vivo* dissolution profiles of the subject pharmaceutical compositions, and the comparison with those of the SINEMET® tablets. It is apparent that the subject compositions consistently deliver steady levels of the exemplary pharmaceutic composition (levodopa and carbidopa in these cases) within the intended effective range (see $C_{max}$), over a longer period of time while avoiding the large / sharp peaks and valleys typically seens in the release profile of SINEMET® tablets (compare AUC and $T_{max}$).

**Example 4** ***Low-shear Wet Granulation of Levodopa, Carbidopa, and Levodopa-Carbidopa***

This example provides exemplary levodopa, carbidopa, and levodopa-carbidopa granules, which were produced with low-shear wet granulation method. The following steps (or minor variations thereof) may be followed to make such granules:

(1) Weighing levodopa or carbidopa, or both levodopa and carbidopa, optionally a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. Granulation fluids were mainly selected from purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, a solution of a polymeric composition in a chlorinated solvent or in a ketone. The granulation was conducted in a small 500-mL cylindrical vessel with manual mixing or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, depending on the batch size.

(4) Drying the wet granulation from step (3), *e.g.*, in a Precision gravity oven, operating at 50 °C, for 8-24 h. Alternatively, the granulation was dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of 50 °C.

(5) Grinding the dried granulation from step (4), *e.g.*, by using a pestle in a mortar, followed by sieving the ground material, *e.g.*, through a U.S. Std. mesh # 60 screen.

(6) Blending the sieved granulation from step (5) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix ready for compression. and

(7) Optionally, passing the lubricated dry mix from step (6) through a sieve or screen, *e.g.*, a U.S. Std. mesh # 60 screen.

**Example 5** ***Low-shear Wet Granulation of a Bioadhesive Polymer, SPHEROMER™ I [p(FASA)] or SPHEROMER™ III***

This example provides exemplary Bioadhesive Polymer, SPHEROMER™ I [p(FASA)] or SPHEROMER™ III granules, which were produced with low-shear wet granulation method. The following steps (or minor variations thereof) may be followed to make such granules:

(1) Weighing the bioadhesive polymer and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. Granulation fluids were mainly selected from a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, a solution of a polymeric composition in a chlorinated solvent or in a ketone. The granulation was conducted in a small cylindrical vessel with manual mixing or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, depending on the batch size.

(4) Drying the wet granulation from step (3), *e.g.*, in a Precision gravity oven, operating at 50 °C, for 8-24 h. Alternatively, the granulation was dried in a fluidized bed drier, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of 55 °C.

(5) Grinding the dried granulation from step (4), *e.g.*, by using a pestle in a mortar, followed by sieving the ground material through a U.S. Std. mesh # 40 screen.

(6) Blending the sieved granulation from step (5) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix ready for compression. and

(7) Optionally, passing the lubricated dry mix from step (6) through a sieve or screen, such as a U.S. Std. mesh # 40 screen.

**Example 6** ***Production of Levodopa, Carbidopa, and Levodopa-Carbidopa Tablets***

This example provides exemplary levodopa, carbidopa, and levodopa-carbidopa tablets, which were produced with direct compression. The following steps (or minor variations thereof) may be followed to make such tablets:

(1) Weighing levodopa or carbidopa, or both levodopa and carbidopa, and or a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, or in a GlobePharma Maxiblend V-shell blended equipped with a 0.5-qt V-shell for 5-15 min, forming a uniform dry mix.

(3) Blending the dry mix from step (2) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

(4) Compressing the lubricated dry mix from step (3), *e.g.*, into tablets, such as by using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. Tablets were prepared at a pressure ranging from 250 to 4000 pounds per square inch (psi) and a compression time of 1 to 4 seconds.

Alternatively, tablets were produced with wet granulation of active ingredients followed by direct compression. The production processes may include the following:

(1) Granulating levodopa or carbidopa, or both levodopa and carbidopa, optionally a bioadhesive polymer composition, and pharmaceutically acceptable excipients in accordance with the method explained in Example 4.

(2) Compressing the lubricated dry granulation mix from step (1) into tablets using a single-station manual tablet press, *e.g.*, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. Tablets were prepared at a pressure ranging from 250 to 4000 pounds per square inch (psi) and a compression time of 1 to 4 seconds.

**Example 7** ***Production of Levodopa-Carbidopa Bilayer Tablets***

This example provides exemplary levodopa-carbidopa bilayer tablets, which were produced with direct compression. The following steps (or minor variations thereof) may be followed to make each tablet layer:

(1) Weighing levodopa or carbidopa, or both levodopa and carbidopa, and or a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(3) Blending the dry mix from step (2) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

Bilayer tablets were produced using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. The compression process included:

(4) Adding the first lubricated layer blend into the die cavity, optionally followed by manually tapping it using a stainless steel spatula.

(5) Adding the second lubricated layer blend into the die cavity.

(6) Pre-compressing the two layers together, *e.g.*, at a pressure ranging from 250 to 500 pounds per square inch (psi) and a compression time of 1 to 5 seconds.

(7) Compressing the pre-compacted layers together, *e.g.*, at a pressure ranging from 1000 to 4000 pounds per square inch (psi) and a compression time of 1 to 4 seconds. Alternatively, bilayer tablets were prepared by first granulating the layer blends followed by blending the granulations with a lubricant in accordance with the method of Example 4, and finally compressing the lubricated layer granulations together into a tablet.

**Example 8** ***Production of Levodopa-Carbidopa Trilayer Tablets***

This example provides exemplary levodopa-carbidopa trilayer tablets, which were produced with direct compression. The following steps (or minor variations thereof) may be followed to make each tablet layer:

(1) Weighing levodopa or carbidopa, or both levodopa and carbidopa, and or a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(3) Blending the dry mix from step (2) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

Trilayer tablets were produced using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. The compression process included:

(4) Adding the first lubricated layer blend into the die cavity, optionally followed by manually tapping it using a stainless steel spatula.

(5) Adding the second lubricated layer blend into the die cavity, optionally followed by manually tapping it together with the first layer using a stainless steel spatula.

(6) Adding the third lubricated layer blend into the die cavity.

(7) Pre-compressing the three layers together, *e.g.*, at a pressure ranging from 200 to 500 pounds per square inch (psi) and a compression time of 1 to 5 seconds.

(8) Compressing the pre-compacted layers together, *e.g.*, at a pressure ranging from 1000 to 4000 pounds per square inch (psi) and a compression time of 1 to 4 seconds. Alternatively, trilayer tablets were prepared by first granulating the layer blends

followed by blending the granulations with a lubricant in accordance with the method of Example 4, and finally compressing the lubricated layer granulations together into a tablet.

**Example 9** ***Production of Levodopa-Carbidopa Quadrilayer Tablets***

This example provides exemplary levodopa-carbidopa quadrilayer tablets, which were produced with direct compression. The following steps (or minor variations thereof) may be followed to make each tablet layer:

(1) Weighing levodopa or carbidopa, or both levodopa and carbidopa, and or a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(3) Blending the dry mix from step (2) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

Quadrilayer tablets were produced using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. The compression process included:

(4) Adding the first lubricated layer blend into the die cavity, optionally followed by manually tapping it using a stainless steel spatula.

(5) Adding the second lubricated layer blend into the die cavity, optionally followed by manually tapping it together with the first layer using a stainless steel spatula.

(6) Adding the third lubricated layer blend into the die cavity, optionally followed by manually tapping it together with the first and second layers using a stainless steel spatula.

(7) Adding the fourth lubricated layer blend into the die cavity.

(8) Pre-compressing the four layers together, *e.g.*, at a pressure ranging from 250 to 500 pounds per square inch (psi) and a compression time of 1 to 5 seconds.

(9) Compressing the pre-compacted layers together, *e.g.*, at a pressure ranging from 1000 to 4000 pounds per square inch (psi) and a compression time of 1 to 4 seconds.

Alternatively, quadrilayer tablets were prepared by first granulating the layer blends

followed by blending the granulations with a lubricant in accordance with the method of Example 4, and finally compressing the lubricated layer granulations together into a tablet.

**Example 10** ***Production of Levodopa-Carbidopa Trilayer Tablets with a Pre-compressed Insert***

This example provides exemplary levodopa-carbidopa trilayer tablets with a pre-compressed insert, which were produced with direct compression. The following steps (or minor variations thereof) may be followed to make each tablet layer:

(1) Weighing levodopa or carbidopa, or both levodopa and carbidopa, and or a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(3) Blending the dry mix from step (2) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

The pre-compressed insert was produced with direct compression and the production processes included:

(4) Weighing levodopa or carbidopa, or both levodopa and carbidopa, and or a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(5) Blending the weighed ingredients from step (4) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(6) Blending the dry mix from step (5) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

(7) Compressing the lubricated mix from step (6) using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. Tablets were prepared, *e.g.*, at a pressure ranging from

500 to 1000 pounds per square inch (psi) and a compression time of, e.g., 1 to 2 seconds.

The trilayer tablets with pre-compressed insert were produced using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. The compression process included:

(8) Adding the first lubricated layer blend into the die cavity, optionally followed by manually tapping it using a stainless steel spatula.

(9) Placing the pre-compressed tablet on the first layer in the center of the die.

(10) Adding the second lubricated layer blend into the die cavity, optionally followed by manually tapping it together with the first layer and the pre-compressed tablet using a stainless steel spatula.

(11) Adding the third lubricated layer blend into the die cavity.

(12) Compressing the three layers together with the pre-compressed insert, *e.g.*, at a pressure ranging from 2000 to 4000 pounds per square inch (psi) and a compression time of 1 to 4 seconds.

The pre-compressed tablet was alternatively placed in the middle of the second layer in the center of the die.

Alternatively, the tablets were prepared by first granulating the layer blends and the pre-compressed tablet ingredients blend followed by mixing the granulations with a lubricant in accordance with the method of Example 4, preparing the pre-compressed insert, and finally compressing the lubricated layer granulations together with the pre-compressed insert into a tablet.

**Example 11** ***Production of Levodopa-Carbidopa Longitudinally Compressed Bioadhesive Multilayer Tablets***

This example provides exemplary levodopa-carbidopa longitudinally compressed bioadhesive multilayer tablets, which were produced with direct compression. Each tablet had at least three layers, longitudinally compressed together, having a cylindrical shape. The trilayer tablet was sealed peripherally with a bioadhesive polymeric composition by compression or heat-sealing technique. The following steps (or minor variations thereof) may be followed to make each tablet layer, including the coating layer:

(1) Weighing levodopa or carbidopa, or both levodopa and carbidopa, or a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(3) Blending the dry mix from step (2) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

Trilayer tablets were produced using, *e.g.*, a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. The compression process included:

(4) Adding the first lubricated layer blend into the die cavity, optionally followed by manually tapping it using a stainless steel spatula.

(5) Adding the second lubricated layer blend into the die cavity, optionally followed by manually tapping it together with the first layer using a stainless steel spatula.

(6) Adding the third lubricated layer blend into the die cavity.

(7) Pre-compressing the three layers together longitudinally into a trilayer tablet at a pressure ranging from 250 to 500 pounds per square inch (psi) and a compression time of 1 to 5 seconds.

(8) Compression-coating of the trilayer tablet from step (7) with the coating layer, *e.g.*, at a pressure ranging from 2000 to 4000 pounds per square inch (psi) and a compression time of, *e.g.*, 1 to 4 seconds.

Alternatively, trilayer tablets were prepared by first granulating the layer blends followed by blending the granulations with a lubricant in accordance with the method of Example 4, and finally compressing the lubricated layer granulations together longitudinally into a tablet.

**Example 12** ***Production of Levodopa-Carbidopa Triple Pressed Tablets***

This example provides exemplary levodopa-carbidopa triple pressed tablets produced with compression of a pre-compressed core tablet with two layers of coating materials. The following steps (or minor variations thereof) may be followed to make each coating layer:

(1) Weighing levodopa or carbidopa, or both levodopa and carbidopa, and or a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(3) Blending the dry mix from step (2) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

The pre-compressed tablet was produced with direct compression and the production processes included:

(4) Weighing levodopa or carbidopa, or both levodopa and carbidopa, and or a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(5) Blending the weighed ingredients from step (4) excluding a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(6) Blending the dry mix from step (5) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

(7) Compressing the lubricated mix from step (6) using, *e.g.*, a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. Tablets were prepared, *e.g.*, at a pressure ranging from 250 to 500 pounds per square inch (psi) and a compression time of, *e.g.*, 1 second.

The pre-compressed tablet was compression-coated, *e.g.*, by the coating layers using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate small and large dies and punch sets. The compression process included:

(8) Adding about half of the first lubricated coating layer blend into the small die cavity.

(9) Placing the pre-compressed tablet on the first half-layer blend in the center of the die.

(10) Adding the second half-layer blend into the die cavity.

(11) Compressing the pre-compressed tablet and the first coating layer together, *e.g.*, at a pressure ranging from 500 to 1000 pounds per square inch (psi) and a compression time of, *e.g.*, 1 second.

(12) Ejecting the double pressed tablet of step (11) from the die.

(13) Adding about half of the second lubricated coating layer blend into the large die cavity.

(14) Placing the double pressed tablet on the first half-layer blend in the center of the die.

(15) Adding the second half-layer blend into the die cavity.

(16) Compressing the double pressed tablet and the second coating layer together, *e.g.*, at a pressure ranging from 2000 to 4000 pounds per square inch (psi) and a compression time of, *e.g.*, 1 to 4 seconds.

Alternatively, the tablets were prepared by first granulating the pre-compressed tablet ingredients blend and coating layer blends followed by mixing the granulations with a lubricant in accordance with the method of Example 4, preparing the pre-compressed tablet, and successive compressing of the pre-compressed tablet with lubricated layer granulations into the final tablet.

**Example 13** ***Production of Levodopa-Carbidopa Pellets with Granulation-Extrusion-Spheronization***

This example provides exemplary levodopa-carbidopa pellets produced with granulation-extrusion-spheronization. The following steps (or minor variations thereof) may be used:

(1) Weighing levodopa and carbidopa, optionally a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending of the weighed ingredients of step (1) in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a dry mix.

(3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. The granulation fluids were mainly selected from, *e.g.*,

purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, a solution of a polymeric composition in a chlorinated solvent or in a ketone.

(4) Extruding the wet granulation from step (3) through the screen of a screen-type extruder, *e.g.*, Caleva Model 20 (or Model 25) Extruder, operating at, *e.g.*, 10-20 rpm, and forming breakable wet strands, the extrudate. The screen aperture was 0.8, 1, or 1.5 mm.

(5) Spheronizing the extrudate from step (4) in a spheronizer, *e.g.*, Caleva Model 250, equipped with a 2.5-mm spheronization plate, operating at, *e.g.*, 1000-2000 rpm for 5-10 min, and forming spheronized pellets.

(6) Drying the spheronized pellets from step (5) in a fluidized bed drier, *e.g.*, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of, *e.g.*, 100-300 lpm (liters per minute) and an inlet air temperature of, *e.g.*, 50°C.

(7) Screening and classifying the dried pellets from step (6) through a stack of stainless steel sieves, U.S. standard mesh sizes 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 45, and 60 using a mechanical sieve shaker, *e.g.*, W.S. Tyler Sieve Shaker Ro-Tap Rx-29, operated for 5 min. Particle size and distribution of pellet formulations were analyzed, and classified pellets ranging from 0.25 mm (mesh # 60) to 2 mm (mesh # 10) were selected for future film coating or other experimentation.

**Example 14** ***Film coating of Levodopa-Carbidopa Pellets***

Levodopa-carbidopa pellets were film-coated with a sub-layer of release rate controlling polymer(s) such as EUDRAGIT® RL 100, EUDRAGIT® RS 100, or mixtures thereof, and with a top-layer of a bioadhesive polymer such as SPHEROMER™ I [p(FASA)], SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof. Optionally, pellets were film-coated with an additional layer of a non-functional polymer such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and polyvinyl alcohol. Polymers were dissolved in different solvent systems depending on their solubility characteristics. The film coating was performed in a fluidized bed coater, Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liter per minute) and an inlet air temperature of 30 °C-35 °C. The pellets were pre-

warmed at 35 °C for 2-5 min and after film-coating were post-dried at 30 °C for 15-30 min.

**Example 15** ***Production of Levodopa-Carbidopa Rapidly Disintegrating Pelletized Tablets***

Rapidly disintegrating pelletized tablets were produced by compression of film-coated spheronized pellets within a carrier matrix. Production processes included the following steps:

(7) Production of levodopa-carbidopa with granulation-extrusion-spheronization in accordance with the method described in Example 13.

(7) Film-coating of a levodopa-carbidopa pellets from step (1) with EUDRAGIT® RL 100, EUDRAGIT® RS 100, or mixtures thereof, in accordance with the method described in Example 14.

(7)Blending of the pre-weighed ingredients of the rapidly disintegrating matrix. The ingredients included levodopa, carbidopa, a superdisintegrant, and pharmaceutically acceptable excipients, excluding a lubricant. Depending on the batch size, blending was carried out, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(7) Blending the dry mix from step (3) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

(7) Blending of the pre-weighed amounts of film-coated pellets from step (2) and lubricated dry mix from step (4), adequate to prepare a single tablet.

(7) Compressing the mixture from step (5) into a tablet, *e.g.*, using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. Tablets were pre-compressed, *e.g.*, at a pressure ranging from 250 to 500 pounds per square inch (psi) for, *e.g.*, 1 to 2 seconds, and subsequently compressed, *e.g.*, at a pressure of 2000 to 4000 psi for, *e.g.*, 1 to 4 seconds.

**Example 16** ***Production of Levodopa-Carbidopa Slowly Eroding Pelletized Trilayer Tablets***

Slowly eroding pelletized multilayer tablets were produced by compression of film-coated spheronized pellets along with three laminated layers; the bottom layer functioning as a passive supporting and optionally bioadhesive layer - the middle layer carrying the film-coated active pellets and eroding slowly, releasing the pellets - and the top layer disintegrating rapidly and releasing its active contents when exposed to aqueous environments. Production processes included the following steps:

(1) Production of levodopa-carbidopa with granulation-extrusion-spheronization in accordance with the method described in Example 13.

(2) Film-coating of a levodopa-carbidopa pellets from step (1) with EUDRAGIT® RL 100, EUDRAGIT® RS 100, or mixtures thereof, in accordance with the method described in Example 14.

(3) Blending of the pre-weighed ingredients of the supporting layer. The ingredients included pharmaceutically acceptable excipients, excluding a lubricant, and optionally a bioadhesive polymer. Depending on the batch size, blending was carried out, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(4) Blending of the pre-weighed ingredients of the immediate release layer. The ingredients included levodopa, carbidopa, a superdisintegrant, and pharmaceutically acceptable excipients, excluding a lubricant. Depending on the batch size, blending was carried out, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(5) Blending of the pre-weighed ingredients of the slow-eroding matrix. The ingredients included pharmaceutically acceptable excipients, excluding a lubricant. Depending on the batch size, blending was carried out, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniform dry mix.

(6) Blending the dry blend from steps (3), (4) and (5) with a lubricant, *e.g.*, using an end-over-end ATR rotator, model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a uniformly lubricated dry mix.

(7) Blending of the pre-weighed amounts of film-coated pellets from step (2) and lubricated slow-eroding layer mix from step (6), adequate to prepare a single tablet.

Trilayer tablets were manufactured using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. The compression process included:

(8) Adding the lubricated supporting layer blend from step (6) into the die cavity, optionally followed by manually tapping it using a stainless steel spatula.

(9) Adding the slow eroding layer blend from step (7) into the die cavity, optionally followed by manually tapping it together with the first layer using a stainless steel spatula.

(10) Adding the lubricated immediate release layer blend from step (6) into the die cavity.

(11) Pre-compressing the three layers together, *e.g.*, at a pressure ranging from 250 to 500 pounds per square inch (psi) and a compression time of, *e.g.*, 1 second.

(12) Compressing the pre-compacted layers together, *e.g.*, at a pressure ranging from 1000 to 4000 pounds per square inch (psi) and a compression time of, *e.g.*, 1 to 4 seconds.

Alternatively, trilayer tablets were prepared by first granulating the layer blends followed by blending the granulations with a lubricant, and finally compressing the lubricated layer granulations together with film-coated pellets into a tablet.

**Example 17** ***Film coating of Levodopa, Carbidopa, and Levodopa-Carbidopa Tablets with Bioadhesive Polymer, SPHEROMER™ III***

Levodopa, carbidopa, and levodopa-carbidopa tablets were film coated with a bioadhesive polymeric composition, SPHEROMER™ III. Bioadhesive SPHEROMER™ III and optionally a functional polymer, or a non-functional polymer, were dissolved in methanol. The film coating was performed in a laboratory pan coater, O'Hara Labcoat, operating at an inlet air flow rate of 60 cfm (cubic foot per min.) and an inlet air temperature of 35 °C. The tablets were pre-warmed at 35 °C for 5-10 min and after film coating were post-dried at 30 °C for 15-30 min.

**Example 18** ***Film coating of Levodopa, Carbidopa, and Levodopa-Carbidopa Tablets with Bioadhesive Polymer, SPHEROMER™ IV***

Levodopa, carbidopa, and levodopa-carbidopa tablets were film coated with a bioadhesive polymeric composition, SPHEROMER™ IV. Bioadhesive SPHEROMER™ IV and optionally a functional polymer, or a non-functional polymer, were dissolved in methanol or a mixture of ethanol and water (3:1 v/v). The film coating was performed in a laboratory pan coater, O'Hara Labcoat, operating at an inlet air flow rate of 60 cfm (cubic foot per minute) and an inlet air temperature of 35 °C. The tablets were pre-warmed at 35 °C for 5-10 min and after film coating were post-dried at 30 °C for 15-30 min.

**Example 19** ***Film coating of Levodopa, Carbidopa, and Levodopa-Carbidopa Tablets with a Functional or a Non-functional Polymer***

Levodopa, carbidopa, and levodopa-carbidopa pellets were film coated with a functional, or with a non-functional polymer. The polymer was dissolved in either of methanol, ethanol, or isopropanol, or their mixture with acetone. The film coating was performed in a laboratory pan coater, O'Hara Labcoat, operating at an inlet air flow rate of 60 cfm (cubic foot per minute) and an inlet air temperature of 30 °C to 40 °C. The tablets were pre-warmed at 30 °C to 40 °C for 2-5 min and after film coating were post-dried at 30 °C to 40 °C for 15-30 min.

**Example 20** ***In vitro Dissolution of Tablet Formulations of Levodopa, Carbidopa, and Levodopa-Carbidopa***

The *in vitro* dissolution profile of levodopa, carbidopa, and levodopa-carbidopa tablet formulations were obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of either of 0.1 N HCl – pH 1.2, phosphate buffer saline (PBS) - pH 4.5, or sodium acetate buffer - pH 4.5 solutions in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by either HPLC or UV spectrophotometry.

**Example 21** ***In vitro Dissolution of SINEMET® 10-100 Tablets, containing 10 mg Carbidopa and 100 mg Levodopa, Lot # 00067***

The *in vitro* dissolution profile of SINEMET® 10-100 tablets, containing 10 mg carbidopa and 100 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of either of 0.1 N HCl - pH 1.2, phosphate buffer saline (PBS) - pH 4.5, or sodium acetate buffer - pH 4.5 solutions, in a USP II

apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The combined dissolution profile of levodopa-carbidopa obtained from UV spectrophotometry analysis is shown in Figure 43.

**Example 22** ***In vitro Dissolution of SINEMET® CR 50-200 Tablets, containing 50 mg Carbidopa and 200 mg Levodopa, Lot # N4682***

The *in vitro* dissolution profile of SINEMET® CR 50-200 tablets, containing 50 mg carbidopa and 200 mg levodopa were obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl - pH 1.2 solution, in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolution profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 44.

**Example 23** ***In vivo Pharmacokinetic Performance of SINEMET® 10-100 Tablets in Fed Beagle Dogs, Lot # 00067***

The *in vivo* performance of SINEMET® 10-100 tablets was evaluated in beagle dogs. SINEMET® tablets were administered to cohorts of six beagle dogs in the fed state and plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 45 shows the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$) and time required to achieve $C_{max}$ ($T_{max}$) are provided in Table 1.

**Table 1.** Pharmacokinetic Data for SINEMET® 10-100 Tablets, Lot # 00067, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$), and time required to achieve $C_{max}$ ($T_{max}$)

| Formulation | AUC (ng/ml.hr) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) |
|---|---|---|---|
| SINEMET® 10-100 Tablets | 5,956 | 3,400 | 0.66 |

**Example 24** ***In vivo Pharmacokinetic Performance of SINEMET® CR 50-200 Tablets***

***in Fed Beagle Dogs, Lot # N4682***

The *in vivo* performance of SINEMET® CR 50-200 tablets was evaluated in beagle dogs. SINEMET® CR tablets were administered to cohorts of six beagle dogs in the fed state and plasma levels of levodopa and carbidopa were measured using HPLC analysis. Figure 46 shows the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$) and time required to achieve $C_{max}$ ($T_{max}$) are provided in Table 2.

**Table 2.** Pharmacokinetic Data for SINEMET® CR 50-200 Tablets, Lot # N4682, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$), and time required to achieve $C_{max}$ ($T_{max}$)

| Formulation | AUC (ng/ml.hr) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) |
|---|---|---|---|
| SINEMET® CR 50-200 Tablets | 3,903 | 1,663 | 2 |

**Example 25** ***In vivo Pharmacokinetic Performance of SINEMET® CR 50-200 Tablets in Fasted Beagle Dogs, Lot # N4682***

The *in vivo* performance of SINEMET® CR 50-200 tablets was evaluated in beagle dogs. SINEMET® CR tablets were administered to cohorts of twelve beagle dogs in the fasted state and plasma levels of levodopa and carbidopa were measured using HPLC analysis. Figure 47 shows the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$) and time required to achieve $C_{max}$ ($T_{max}$) are provided in Table 3.

**Table 3.** Pharmacokinetic Data for SINEMET® CR 50-200 Tablets, Lot # N4682, in Fasted Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$), and time required to achieve $C_{max}$ ($T_{max}$)

| Formulation | AUC (ng/ml.hr) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) |
|---|---|---|---|
| SINEMET® CR 50-200 Tablets | 936 | 604 | 1 |

**Example 26** ***Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets, Lot # 505-065***

Bioadhesive levodopa-carbidopa trilayer tablets were produced with direct compression in accordance with the method described in Example 8. Tablets comprised an active controlled release (CR) layer laminated between two passive bioadhesive layers. The weight and composition of the CR and bioadhesive layers are given in Table 4.

**Table 4.** Weight and Composition of Controlled Release and Bioadhesive Layers of Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablet, Lot # 505-065

| **Controlled Release Layer** | | |
|---|---|---|
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 47.0 | 200.0 |
| Carbidopa monohydrate, USP | 12.7 | 54.0 |
| Hypromellose 2208, 100 cps, USP | 19.7 | 83.6 |
| Hypromellose 2910, 5 cps, USP | 9.8 | 41.8 |
| L-Glutamic acid, FCC | 4.9 | 20.8 |
| Corn Starch, NF | 4.9 | 20.8 |
| Magnesium Stearate, NF | 1.0 | 4.2 |
| **Total** | 100.0 | 425.2 |
| **Bioadhesive Layer** | | |
| **Ingredients** | **Weight %** | **Weight (mg)** |
| SPHEROMER™ III | 98.0 | 245.0 |
| Ethylcellulose (ETHOCEL™ Std 100 FP), NF | 1.0 | 2.5 |
| Magnesium Stearate, NF | 1.0 | 2.5 |
| **Total** | 100.0 | 250.0 |

The ingredients of the CR and bioadhesive layers excluding magnesium stearate

were blended on the ATR rotator end-over-end for 5 min. Magnesium stearate was added to the ingredients blend of each layer and the materials were blended for an additional 5 min. A 0.3287" x 0.8937" capsule-shaped die and punch set was installed on GlobePharma Manual Tablet Compaction Machine MTCM-I. The CR and two bioadhesive layers were pre-compressed together at a pressure of 200 psi (pound per square inch) for 5 seconds and then pressed at 3000 psi for 1 sec.

**Example 27** ***In vitro Dissolution and in vivo Pharmacokinetic Performance of Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets, Lot # 505-065***

The *in vitro* dissolution profile of bioadhesive levodopa-carbidopa trilayer tablets, containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolu-tion profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 48.

The *in vivo* performance of bioadhesive levodopa-carbidopa trilayer tablets was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed state. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 49 shows the plasma concentration profiles of levodopa and carbidopa in the fed state. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$) and time required to achieve $C_{max}$ ($T_{max}$) are provided in Table 5.

**Table 5.** Pharmacokinetic Data for Bioadhesive Levodopa-Carbidopa Trilayer Tablets, Lot # 505-065, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$), and time required to achieve $C_{max}$ ($T_{max}$)

| Fasting Period | AUC (ng/ml.hr) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) |
|---|---|---|---|
| Fed | 7,782 | 1,918 | 4.2 |

**Example 28** ***Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets, Lot # 505-066***

Bioadhesive levodopa-carbidopa trilayer tablets were produced with direct compression in accordance with the method described in Example 8. Tablets comprised an active controlled release (CR) layer laminated between two passive bioadhesive layers. The weight and composition of the CR and bioadhesive layers are given in Table 6.

**Table 6.** Weight and Composition of Controlled Release and Bioadhesive Layers of Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablet, Lot # 505-066

| **Controlled Release Layer** | | |
|---|---|---|
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 42.9 | 200.0 |
| Carbidopa monohydrate, USP | 11.6 | 54.0 |
| Hypromellose 2208, 100 cps, USP | 35.8 | 167.2 |
| Hypromellose 2910, 5 cps, USP | 4.5 | 20.9 |
| L-Glutamic acid, FCC | 2.2 | 10.4 |
| Corn Starch, NF | 2.2 | 10.4 |
| Magnesium Stearate, NF | 0.8 | 3.8 |
| **Total** | 100.0 | 466.7 |
| **Bioadhesive Layer** | | |
| **Ingredients** | **Weight %** | **Weight (mg)** |
| SPHEROMER™ III | 98.0 | 245.0 |
| Ethylcellulose (ETHOCEL™ Std 100 FP), NF | 1.0 | 2.5 |
| Magnesium Stearate, NF | 1.0 | 2.5 |
| **Total** | 100.0 | 250.0 |

The ingredients of the CR and bioadhesive layers excluding magnesium stearate were blended on the ATR rotator end-over-end for 5 min. Magnesium stearate was added to the ingredients blend of each layer and the materials were blended for an additional 5 min. A 0.3287" x 0.8937" capsule-shaped die and punch set was installed on GlobePharma Manual Tablet Compaction Machine MTCM-I. The CR and two bioadhesive layers were

pre-compressed together at a pressure of 200 psi (pound per square inch) for 5 seconds and then pressed at 3000 psi for 1 sec. - -

**Example 29** ***In vitro Dissolution and in vivo Pharmacokinetic Performance of Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets, Lot # 505-066***

The *in vitro* dissolution profile of bioadhesive levodopa-carbidopa trilayer tablets, containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolu-tion profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 50.

The *in vivo* performance of bioadhesive levodopa-carbidopa trilayer tablets was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed state. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 51 shows the plasma concentration profiles of levodopa and carbidopa in the fed state. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$) and time required to achieve $C_{max}$ ($T_{max}$) are provided in Table 7.

**Table 7.** Pharmacokinetic Data for Bioadhesive Levodopa-Carbidopa Trilayer Tablets, Lot # 505-066, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$), and time required to achieve $C_{max}$ ($T_{max}$)

| Fasting Period | AUC (ng/ml.hr) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) |
|---|---|---|---|
| Fed | 8,537 | 1,584 | 3.5 |

**Example 30** ***Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets, Lot # 506-063***

Bioadhesive levodopa-carbidopa trilayer tablets were produced with direct compression in accordance with the method described in Example 8. Tablets comprised an

active controlled release (CR) layer laminated between a passive bioadhesive layer and an active immediate release (IR) layer. The weight and composition of the IR, CR and bioadhesive layers are given in Table 8.

**Table 8.** Weight and Composition of Immediate Release, Controlled Release, and Bioadhesive Layers of Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablet, Lot # 506-063

| **Immediate Release Layer** | | |
|---|---|---|
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 26.67 | 40.00 |
| Carbidopa monohydrate, USP | 7.20 | 10.80 |
| LUDIPRESS® | 65.63 | 98.45 |
| Magnesium Stearate, NF | 0.50 | 0.75 |
| **Total** | 100.00 | 150.00 |
| | | |
| **Controlled Release Layer** | | |
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 40.00 | 160.00 |
| Carbidopa monohydrate, USP | 10.79 | 43.16 |
| Hypromellose 2208, 100 cps, USP | 38.00 | 152.00 |
| Hypromellose 2910, 5 cps, USP | 4.71 | 18.84 |
| L-Glutamic acid, FCC | 3.00 | 12.00 |
| Corn Starch, NF | 3.00 | 12.00 |
| Magnesium Stearate, NF | 0.50 | 2.00 |
| **Total** | 100.00 | 400.00 |
| | | |
| **Bioadhesive Layer** | | |
| **Ingredients** | **Weight %** | **Weight (mg)** |
| SPHEROMER™ III | 98.0 | 147.00 |
| Ethylcellulose (ETHOCEL™ Std 100 FP), NF | 1.50 | 2.25 |
| Magnesium Stearate, NF | 0.50 | 0.75 |
| **Total** | 100.00 | 150.00 |

The ingredients of the IR, CR and bioadhesive layers excluding magnesium stearate were blended on the ATR rotator end-over-end for 5 min. Magnesium stearate was added to the ingredients blend of each layer and the materials were blended for an additional 5 min. A 0.4375" standard convex-shaped die and punch set was installed on GlobePharma Manual

Tablet Compaction Machine MTCM-I. The trilayer tablet was prepared by compression at 2000 psi for 1 second.

**Example 31** ***In vitro Dissolution and in vivo Pharmacokinetic Performance of Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets, Lot # 506-063***

The *in vitro* dissolution profile of bioadhesive levodopa-carbidopa trilayer tablets, containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolu-tion profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 52.

The *in vivo* performance of bioadhesive levodopa-carbidopa trilayer tablets was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed state. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 53 shows the plasma concentration profiles of levodopa and carbidopa in the fed state. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$) and time required to achieve $C_{max}$ ($T_{max}$) are provided in Table 9.

**Table 9.** Pharmacokinetic Data for Bioadhesive Levodopa-Carbidopa Trilayer Tablets, Lot # 506-063, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$), and time required to achieve $C_{max}$ ($T_{max}$)

| Fasting Period | AUC (ng/ml.hr) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) |
|---|---|---|---|
| Fed | 5,445 | 1,473 | 5.7 |

**Example 32** ***Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets with Pre-compressed Insert, Lot # 506-024***

Bioadhesive levodopa-carbidopa trilayer tablets with pre-compressed insert were produced with direct compression in accordance with the method described in Example 10.

Tablets comprised a rapidly disintegrating pre-compressed insert embedded in an active controlled release (CR) layer laminated between a passive bioadhesive layer and an active immediate release (IR) layer. The weight and composition of the pre-compressed insert, and CR, IR and bioadhesive layers are given in Table 10.

**Table 10.** Weight and Composition of Pre-compressed Insert, and Controlled Release, Immediate Release and Bioadhesive Layers of Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablet, Lot # 506-024

| Pre-compressed Insert | | |
|---|---|---|
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 23.53 | 40.00 |
| Carbidopa monohydrate, USP | 6.35 | 10.80 |
| LUDIPRESS® | 69.68 | 118.45 |
| Magnesium Stearate, NF | 0.44 | 0.75 |
| **Total** | 100.00 | 170.00 |

| Controlled Release Layer | | |
|---|---|---|
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 42.86 | 120.00 |
| Carbidopa monohydrate, USP | 11.57 | 32.40 |
| Hypromellose 2208, 100 cps, USP | 38.04 | 106.50 |
| Hypromellose 2910, 5 cps, USP | 2.29 | 6.40 |
| L-Glutamic acid, FCC | 2.21 | 6.20 |
| Corn Starch, NF | 2.21 | 6.20 |
| Magnesium Stearate, NF | 0.82 | 2.30 |
| **Total** | 100.00 | 280.00 |

| Immediate Release Layer | | |
|---|---|---|
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 26.67 | 40.00 |
| Carbidopa monohydrate, USP | 7.20 | 10.80 |
| LUDIPRESS® | 65.63 | 98.45 |
| Magnesium Stearate, NF | 0.50 | 0.75 |
| **Total** | 100.00 | 150.00 |

| Bioadhesive Layer | | |
|---|---|---|
| **Ingredients** | **Weight %** | **Weight (mg)** |
| SPHEROMER™ III | 98.0 | 147.00 |
| Ethylcellulose (ETHOCEL™ Std 100 FP), NF | 1.50 | 2.25 |
| Magnesium Stearate, NF | 0.50 | 0.75 |
| **Total** | 100.00 | 150.00 |

The ingredients of the insert, and CR, IR and bioadhesive layers excluding magnesium stearate were blended on the ATR rotator end-over-end for 5 min. Magnesium stearate was added to the ingredients blend of each layer and the materials were blended for an additional 5 min. A 0.2618" standard convex-shaped die and punch set was installed on GlobePharma Manual Tablet Compaction Machine MTCM-1. The ingredients blend of the

insert was compressed into a tablet at 500 psi (pound per square inch) for 1 second. A 0.4375" standard convex-shaped die and punch set was installed on the same tablet compactor. The trilayer tablet was prepared by compression at 3000 psi for 1 second.

**Example 33** ***In vitro* Dissolution and *In vivo* Pharmacokinetic Performance of Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets with Pre-compressed Insert, Lot # 506-024**

The *in vitro* dissolution profile of bioadhesive levodopa-carbidopa trilayer tablets with pre-compressed insert, containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolution profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 54.

The *in vivo* performance of bioadhesive levodopa-carbidopa trilayer tablets with pre-compressed insert was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed state. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 55 shows the plasma concentration profiles of levodopa and carbidopa in the fed state. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$) and time required to achieve $C_{max}$ ($T_{max}$) are provided in Table 11.

**Table 11.** Pharmacokinetic Data for Bioadhesive Levodopa-Carbidopa Trilayer Tablets with Pre-compressed Insert, Lot # 506-024, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$), and time required to achieve $C_{max}$ ($T_{max}$)

| Fasting Period | AUC (ng/ml.hr) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) |
|---|---|---|---|
| Fed | 8,104 | 1,782 | 2.3 |

**Example 34** ***Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets with Pre-compressed Insert, Lot # 507-027***

Bioadhesive levodopa-carbidopa trilayer tablets with pre-compressed insert were

produced with direct compression in accordance with the method described in Example 10. Tablets comprised a rapidly disintegrating pre-compressed insert embedded in an active controlled release (CR) layer laminated between a passive bioadhesive layer and an active immediate release (IR) layer. The weight and composition of the pre-compressed insert, and CR, IR and bioadhesive layers are given in Table 12.

**Table 12.** Weight and Composition of Pre-compressed Insert, and Controlled Release, Immediate Release and Bioadhesive Layers of Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablet, Lot # 507-027

| Pre-compressed Insert | | |
|---|---|---|
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 40.00 | 40.00 |
| Carbidopa monohydrate, USP | 10.80 | 10.80 |
| LUDIPRESS® LCE | 48.60 | 48.60 |
| Magnesium Stearate, NF | 0.50 | 0.50 |
| **Total** | 100.00 | 100.00 |
| | | |
| **Controlled Release Layer** | | |
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 34.29 | 120.00 |
| Carbidopa monohydrate, USP | 9.26 | 32.40 |
| Hypromellose 2208, 100 cps, USP | 42.14 | 147.50 |
| Hypromellose 2208, 4000 cps, USP | 7.71 | 27.00 |
| L-Glutamic acid, FCC | 3.00 | 10.50 |
| Corn Starch, NF | 3.00 | 10.50 |
| Magnesium Stearate, NF | 0.60 | 2.10 |
| **Total** | 100.00 | 350.00 |
| | | |
| **Immediate Release Layer** | | |
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 26.67 | 40.00 |
| Carbidopa monohydrate, USP | 7.20 | 10.80 |
| LUDIPRESS® | 65.63 | 98.45 |
| Magnesium Stearate, NF | 0.50 | 0.75 |
| **Total** | 100.00 | 150.00 |
| | | |
| **Bioadhesive Layer** | | |
| **Ingredients** | **Weight %** | **Weight (mg)** |
| SPHEROMER™ III | 98.00 | 147.00 |
| Ethylcellulose (ETHOCEL™ Std 100 FP), NF | 1.50 | 2.25 |
| Magnesium Stearate, NF | 0.50 | 0.75 |
| **Total** | 100.00 | 150.00 |

The ingredients of the insert, and CR, IR and bioadhesive layers excluding magnesium stearate were blended on the ATR rotator end-over-end for 5 min. Magnesium stearate was added to the ingredients blend of each layer and the materials were blended for an additional 5 min. A 0.2618" standard convex-shaped die and punch set was installed on GlobePharma Manual Tablet Compaction Machine MTCM-I. The ingredients blend of the

insert was compressed into a tablet at 500 psi (pound per square inch) for 1 second. A 0.4375" standard convex-shaped die and punch set was installed on the same tablet compactor. The trilayer tablet was prepared by compression at 3500 psi for 1 second.

**Example 35** ***In vitro Dissolution and In vivo Pharmacokinetic Performance of Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets with Pre-compressed Insert, Lot # 507-027***

The *in vitro* dissolution profile of bioadhesive levodopa-carbidopa trilayer tablets with pre-compressed insert, containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolution profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 56.

The *in vivo* performance of bioadhesive levodopa-carbidopa trilayer tablets with pre-compressed insert was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed state. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 57 shows the plasma concentration profiles of levodopa and carbidopa in the fed state. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$) and time required to achieve $C_{max}$ ($T_{max}$) are provided in Table 13.

**Table 13.** Pharmacokinetic Data for Bioadhesive Levodopa-Carbidopa Trilayer Tablets with Pre-compressed Insert, Lot # 507-027, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$), and time required to achieve $C_{max}$ ($T_{max}$)

| Fasting Period | AUC (ng/ml.hr) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) |
|---|---|---|---|
| Fed | 9,597 | 1,742 | 4.2 |

**Example 36** ***Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Triple Pressed Tablets, Lot # 507-047***

Bioadhesive levodopa-carbidopa triple pressed tablets were produced with direct compression in accordance with the method described in Example 12. Tablets comprised a pre-compressed active inner core, press-coated with an erodible bioadhesive controlled-release (CR) layer overlaid by an immediate-release (IR) layer. The weight and composition of the IR and CR layers, and the inner core are given in Table 14.

**Table 14.** Weight and Composition of Immediate Release and Bioadhesive Controlled Release Layers, and the Inner Core of Levodopa-Carbidopa 200 mg/50 mg Triple Pressed Tablet, Lot # 507-047

| **Immediate Release Layer (Outer Layer)** | | |
|---|---|---|
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 16.00 | 40.00 |
| Carbidopa monohydrate, USP | 4.32 | 10.80 |
| LUDIPRESS® | 79.18 | 247.95 |
| Magnesium Stearate, NF | 0.50 | 1.25 |
| **Total** | 100.00 | 300.00 |
| | | |
| **Controlled Release Layer (Middle Layer)** | | |
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 40.00 | 120.00 |
| Carbidopa monohydrate, USP | 10.80 | 32.39 |
| Polyethylene Oxide (Polyox™ WSR-301), NF | 47.70 | 143.11 |
| L-Glutamic acid, FCC | 1.00 | 3.00 |
| Magnesium Stearate, NF | 0.50 | 1.50 |
| **Total** | 100.00 | 300.00 |
| | | |
| **Fast Disintegrating Core (Inner Core)** | | |
| **Ingredients** | **Weight %** | **Weight (mg)** |
| Levodopa, USP | 40.00 | 40.00 |
| Carbidopa monohydrate, USP | 10.80 | 10.80 |
| LUDIPRESS® LCE | 48.70 | 48.70 |
| Magnesium Stearate, NF | 0.50 | 0.50 |
| **Total** | 100.00 | 100.00 |

The ingredients of the IR and CR layers and the inner core excluding magnesium stearate were blended on the ATR rotator end-over-end for 5 min. Magnesium stearate was

added to the ingredients blend of each layer and the materials were blended for an additional 5 min. A 0.2400" standard convex-shaped die and punch set was installed on GlobePharma Manual Tablet Compaction Machine MTCM-I. The ingredients blend of the inner core was compressed into a tablet at 250 psi (pound per square inch) for 1 second. A 0.3228" standard convex-shaped die and punch set was installed on the same tablet compactor. The inner core was press-coated with the CR layer blend by compression at 500 psi for 1 second. A 0.4375" standard convex-shaped die and punch set was installed on the same tablet compactor. The double pressed tablet prepared above, was press-coated with the IR layer blend by compression at 4000 psi for 1 second.

**Example 37** ***In vitro Dissolution and In vivo Pharmacokinetic Performance of Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Triple Pressed Tablets, Lot # 507-047***

The *in vitro* dissolution profile of levodopa-carbidopa triple pressed tablets, containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolution profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 58.

The *in vivo* performance of levodopa-carbidopa triple pressed tablets was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed state. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 59 shows the plasma concentration profiles of levodopa and carbidopa in the fed state. The pharma-cokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$) and time required to achieve $C_{max}$ ($T_{max}$) are provided in Table 15.

**Table 15.** Pharmacokinetic Data for Levodopa-Carbidopa Triple Pressed Tablets, Lot # 507-047, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration ($C_{max}$), and time required to achieve $C_{max}$ ($T_{max}$)